# FIVE-MEMBERED RING SYNTHESIS BY THE FREE RADICAL PROMOTED COUPLING OF UNSATURATED CARBON CENTERS

BY

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In loving memory of Chanel

## ACKNOWLEDGEMENTS

Robert E. Lee once said, "It is well that war is so terrible, lest we become fond of it." I believe that this thought is equally true of graduate school. I have fought, cried and laughed with many people that I met during my stay here, and it is safe to say that although graduate school has not always been pleasant, it has been a great experience and I have gained a lot. There are many people have helped me through difficult times and in one way or another helped me grow into a better person, both professionally and personally.

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of the University of Florida in Partial Fulfillment of the
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# FIVE-MEMBERED RING SYNTHESIS BY THE FREE RADICAL PROMOTED COUPLING OF UNSATURATED CARBON CENTERS

By

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This dissertation investigated the metal-induced free radical reactions of tributyltin hydride (TBTH) and samarium diiodide ($SmI_2$), using carbon-centered radical precursors prepared from alkynes, alkenes, aldehydes, ketones, and enones. The unsaturated carbon centers of these functionalities were tethered to a variety of radical acceptors, including oxime ethers, $\alpha,\beta$-unsaturated esters, styrene segments, and unactivated olefins. Three related investigations collectively examined the free radical reactions of the above free radical precursors and acceptors in an attempt to further understand the synthetic utility of free radicals in cyclization reactions.

The first area studied was the intramolecular coupling of an acetylene, a radical precursor, with an oxime ether, a radical acceptor. The hydrostannation-type reaction produced a functionalized cyclopentane ring with an exocyclic-methylene functionality and a protected amino group; excellent yields resulted, ranging from 56% to 95%. This was the first

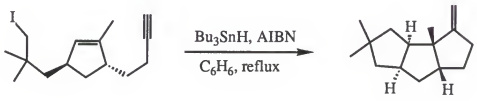
study to combine the unsaturated systems of an acetylene and an oxime ether and should have general applicability in natural product synthesis.

The second area of study investigated the intramolecular coupling of aldehyde and ketone carbonyls to α,β-unsaturated esters and styrene systems. A tin "ketyl," is formed when a tributyltin radical adds to the oxygen of a carbonyl; our seminal investigations indicate that the "ketyl" easily cyclizes onto activated olefins. The objective was to investigate whether the radical formed after the first cyclization could participate in additional tandem ring forming reactions. Thus, various substrates containing an aldehyde or a ketone carbonyl and a suitably appended olefin were subjected to standard free radical conditions. In some cases,only one cyclization occurred, and monocyclic products were isolated. The yields of the systems which did undergo the tandem cyclizations, however, were generally good, and resulted in substituted polycyclic products.

The final chapter was the first study to compare the metal ketyls of tin and samarium from a synthetic perspective. A series of substrates from the previous study were subjected to a reaction with samarium diiodide, a one electron reductant. Striking differences between the two methodologies were noted, and it appears that in some cases, the samarium may act by a different mechanism than that of tin.

# CHAPTER 1
# INTRODUCTION

In the past, the use of carbon centered free radicals was unexploited by the synthetic organic chemist and was limited to the area of polymer chemistry.[1] It was believed then that the free radical was too unruly or nonspecific to be used in the highly-controlled world of synthetic methodology. However, the use of free radicals has recently become an integral part of many well-designed syntheses.[2] For example, in the landmark synthesis of hirsutene (2), Curran and Rakiewicz[3] demonstrated that a free radical could be used to generate complex ring systems, as shown in Scheme 1-1.




1 2

Scheme 1-1

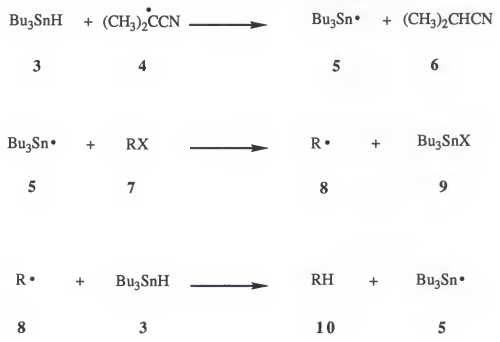
The linear triquinane was produced in a single step from a tandem sequence commencing with the generation of a 5-hexenyl radical from primary iodide 1 which was captured by the olefin and finally terminated by addition to the suitably disposed acetylene. It is evident from Curran and Rakiewicz's work that free radical cyclization reactions are well suited for use in the synthesis of natural products, and in some cases they provide a simple solution to a difficult synthetic problem.

This dissertation will focus on the application of free radicals in the synthesis of simple and complex ring systems. In three separate, but related methodology studies, the scope and limitations of the intramolecular free radical coupling of unsaturated carbon centers were examined. Five-membered rings were formed in these reactions as either single rings or as components in bicyclic systems. The majority of the reactions were successful and provide new insight in the synthetic utility of free radicals in cyclization reactions.

The term "free radical" applies to species which possess one unpaired electron.[2] Free radicals are highly reactive intermediates and the majority of free radical reactions occur at diffusion controlled rates.[2] In fact, many reactions must be controlled by dilution to maintain a low concentration of free radicals throughout the reaction in order to prevent undesirable side reactions. Additionally, free radicals can react with themselves or engage in a whole host of reactions that cannot be accomplished by cations or anions.

Free radical reactions also have other benefits. They generally embrace mild reaction conditions in contrast to the harsh reaction conditions of cations or anions.[2] This makes them an attractive synthetic alternative because the delicate structural features of functionalized reactants, often lacking protecting groups, may not be compatible with the vigorous reaction conditions associated with the generation of anions or cations. Additionally, the regio-, stereo- and chemoselectivities of some free radical reactions are high and predictable.[4] So, free radicals, once thought to be too "unruly," can now be used in synthesis today to give predictable products.

There are two broad classes of free radical reactions: atom or group abstraction (Scheme 1-2) and free radical addition to multiple bonds (Scheme 1-3).[2(c)] The most common abstracted atoms are halogens; phenyl selenides and thiocarbonyl compounds may also serve as radical precursors. The reduction of halides, mechanistically shown in Scheme 1-2, occurs though a chain radical mechanism beginning with the thermal generation of 4 from azobisisobutylnitrile. Radical 4 abstracts a hydrogen atom from TBTH (3) to give radical 5. It is this radical (5) which abstracts the halogen atom from halide 7 to give carbon centered radical 8. Radical 8 then abstracts a hydrogen atom from another molecule of TBTH (3) generating the reduced compound 10 and another molecule of 5 and the cycle is repeated.




Scheme 1-2

In the case where the radical simply adds to an unsaturated center (Scheme 1-3), the radical character is not destroyed during the course of the reaction because free radical 11 reacts with a nonfree radical 12 to form another radical (13) to continue the chain process.

**11** **12** **13**

Scheme 1-3

It is widely accepted that while the addition of a carbon centered radical to a multiple bond is reversible,[2] it can also be an energetically favorable process; the C-C σ bond is formed from a C-C π bond and it is a very exothermic reaction.[2(a)] Giese noted that the substituents on the alkene in this reaction may affect the rate of addition,[2(a)] and this process can be described by the simplified frontier molecular orbital (FMO) diagrams in Figures 1-1 and 1-2, discussed next.

The singly occupied molecular orbital (SOMO) of the radical interacts with either the lowest unoccupied molecular orbital (LUMO) (Figure 1-1) or the highest occupied molecular orbital (HOMO) (Figure 1-2) of the unsaturated system.[5] Any substituent on either the free radical or the π-bond which lowers the difference in energy between the SOMO and the LUMO or the SOMO and the HOMO serves to increase the likelihood of the reaction. Electron withdrawing substituents on the π-bond lower the LUMO and electron donating substituents increase the HOMO.[5] Radicals which possess electron donating substituents are termed nucleophilic and have high lying SOMOs;[5] radicals which possess electron withdrawing

substituents, and subsequently have low lying SOMOs are termed electrophilic.[5] Nucleophilic radicals, such as ketyls, interact readily with the LUMO of unsaturated systems (Figure 1-1); however, electrophilic radicals with low lying SOMOs preferentially interact with the HOMO of unsaturated systems (Figure 1-2).[2(a), 6] Thus, a favorable interaction between the two orbitals is necessary for the addition to occur.

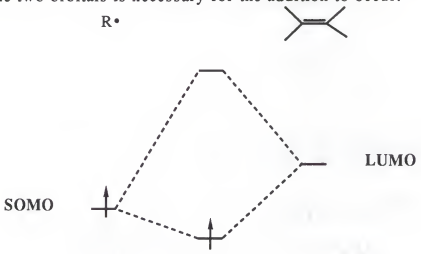



Figure 1-1

Orbital interaction of a nucleophilic radical

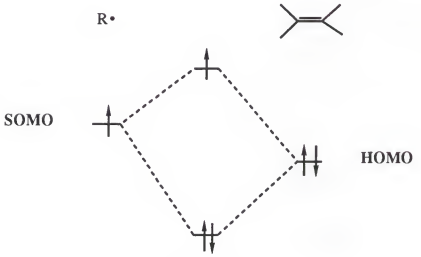
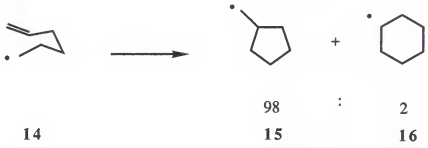



Figure 1-2

Orbital interaction of an electrophilic radical

Free radicals are particularly useful in the formation of 5-membered rings. The cyclizations of the 5-hexenyl radical (14) (Scheme 1-4) have been extensively studied and proceed in a highly regioselective manner.[6] In almost all cases, the 5-hexenyl (or 5-hexnyl in the case of an acetylene) radicals preferentially engages in 5-exo cyclizations. The reaction follows Baldwin's predictions,[7] and cyclopentyl radical 15 is formed faster than the cyclohexyl radical 16 (Scheme 1-4) in a ratio of 50:1.[6] According to Beckwith,[6] the addition of the radical proceeds through a chair transition state (14), with any substituents preferring pseudoequatorial positions on the ring. The stereoselectivity observed on these ring closure reactions with mono-substituted substrates is also best explained by this transition state with substituents occupying the pseudoequatorial positions in 14.




Scheme 1-4

There are many ways to generate radicals; they are ubiquitous in nature and are easily formed under photolytic conditions. Tributyltin hydride (TBTH) and samarium diiodide ($SmI_2$) are two reagents we used to produce free radicals. TBTH is a "classical" free radical reagent and when subjected to an initiator, such as azobisisobutylnitrile (AIBN), it engages in a free radical chain mechanism to yield products.[8] Samarium diiodide,

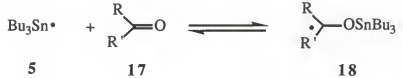
on the other hand, is simply a stoichiometric one-electron redox reductant and it donates a electron into the system; however, two one-electron transfers occur and therefore two equivalents of $SmI_2$ are generally required for each transformation.[9] This dissertation will examine the one electron coupling of unsaturated precursors by TBTH in Chapters 2 and 3 and $SmI_2$ in Chapter 4.

Tributyltin hydride is a traditional reagent; it has been known for over 20 years that it engages in free radical reactions.[8] The application of this reagent in synthesis is so extensive that much attention has been devoted to its utilization.[10] It is commercially available or it is easily prepared from the redox reaction of bistributyltin oxide and polymethylhydroxy siloxane[11] as well as from other simple procedures.[12] It is easily stored, has a reasonable shelf life, and it is not excessively toxic.[10] Tin has a $5s^25p^2$ electronic configuration and organotin (IV) compounds exist in the tetrahedral $sp^3$ hybridization. Tributyltin hydride possesses a very long tin-hydrogen bond (0.17 nm)[10] and is easily homolytically cleaved either photochemically or thermally with an initiator to generate the tributyltin radical. It is this radical that is responsible for inducing the free radical sequences discussed below.

TBTH engages in a whole host of reactions, including reduction of carbonyls, acetylenes and halides. The mechanism of reduction of halides, as shown in Scheme 1-2, involves the trapping of the radical 8 with a hydrogen atom from a molecule of tributyltin hydride (3). The simple reduced product 10 is formed and another molecule of tributyltin radical (5) continues the chain mechanism. Additional studies indicate that the generation of a radical such as 8 may be followed by intramolecular (or

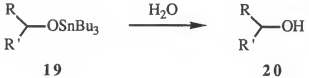
intermolecular) coupling to an alkene[13] or alkyne,[14] thus broadening the synthetic possibilities of group abstraction.

The reduction of carbonyls (Scheme 1-5) and acetylenes (Scheme 1-6), with the tributyltin radical (5) differs from the above process of halide reduction in that the tributyltin radical adds to the unsaturated system. In the reaction with carbonyls, the tin radical adds to the oxygen atom of the carbon-oxygen double bond[15] (17) and creates a tin alkoxy radical 18. This "ketyl" radical can engage in a variety of additional reactions, or it simply may react again with TBTH and create tin alkoxide 19.




5 17 18


18 3 19 5

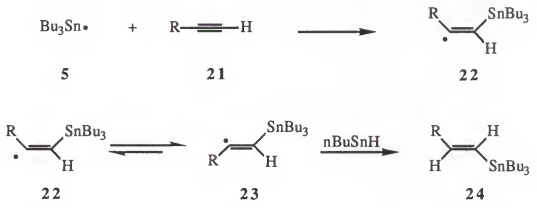



19 20

Scheme 1-5

The free alcohol is finally obtained when the tin alkoxide 19 is quenched with water.

In a similar reaction with acetylenes, the tributyltin radical 5 adds to the terminus of the triple bond in 21 forming a vinyl-stannyl radical 22.[16] The vinyl-stannyl radical, can equilibrate to trans radical 23, and then react with a hydrogen atom from another molecule of TBTH to give the hydrostannylated product 24. The vinyl stannyl radical can also add to a free radical acceptor to create vinyl-stannyl products. As demonstrated in the above examples, TBTH is extremely versatile and reacts selectively with a number of functional groups to form a variety of products.

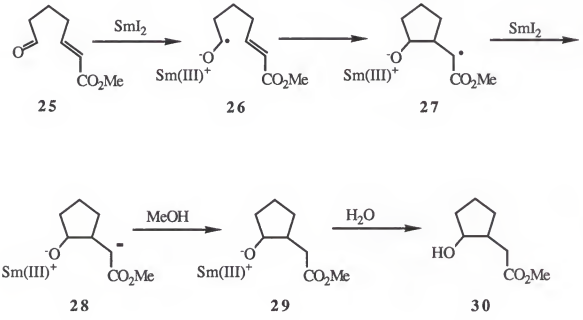



Scheme 1-6

Samarium diiodide is also versatile reagent; it engages in some reactions similar to those of TBTH. First introduced by Namy et al.[17] in 1977, this compound has seen a rapid increase in its applicability to synthesis.[18] This dark blue-green reagent is commercially available or it is easily prepared in tetrahydrofuran from samarium metal and methylene diiodide.[17] It is a powerful reducing agent[19] and acts either through a radical or anionic pathway. The latter is really a two-step process involving two full equivalents of $SmI_2$, and resulting in a two electron net

reduction.[20] Sm(II) reductions are very mild and often done at low temperatures. There is often considerable stereocontrol, presumably due to the oxophilic nature of samarium.[17]

The mechanism of the samarium diiodide reductions is quite different from that of tributyltin hydride: $SmI_2$ is oxidized to Sm(III) when it donates an electron to a carbonyl. Quite a number of reactions of $SmI_2$ involve an initial one-electron reduction of a carbonyl. The strong oxophilic nature of the samarium atom guides its reactivity and it is generally accepted that the $SmI_2$ interacts with the carbonyl, forming a "ketyl-like" radical[21] (26), shown in Scheme 1-7.

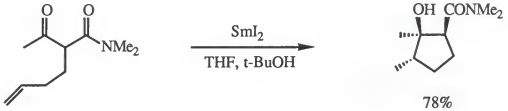



Scheme 1-7

Work performed in our group[22] demonstrated that Sm (III) ketyls can add to a pendant olefin in 26 to form 27. Intermediate (27) is further reduced by an additional equivalent of $SmI_2$ to give anion 28 which reacts

with a proton source present in the reaction mixture to form 29. Alcohol 30 is finally formed during aqueous workup. Because the majority of reactions of samarium diiodide involve two one-electron transfers, it is this last additional one-electron reduction which mechanistically differs markedly from TBTH reductions and may cause substantially different products to form.

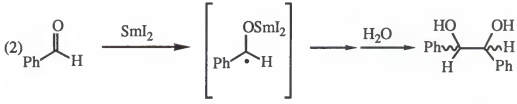
The free radical nature of $SmI_2$ may not be apparent from the above example; an anion can also add to an activated olefin in a Michael fashion. But, the "ketyl-like" radical formed from the addition of $SmI_2$ to a carbonyl can also cyclize onto a nonactivated olefin in 31 as shown in Scheme 1-8.[23]




31 32

Scheme 1-8

Additionally, Namy et al.[24] noted the free radical nature of this reagent when he observed that when benzaldehyde (33) was treated with $SmI_2$ without a proton source, pinacol product 35 (Scheme 1-9) was formed.[25]

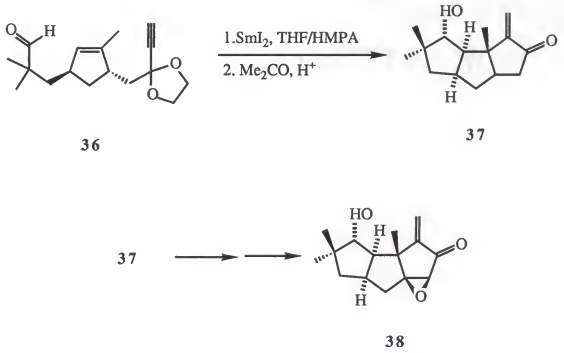



33 34 35

Scheme 1-9

The initial presence of a free radical is suggested; an anion could not cyclize onto a nonactivated olefin or form pinacol-type products.[26]

The synthesis of hypnophilin (38) by Fevig et al., provides an elegant application of this reagent in the total synthesis of natural products (Scheme 1-10).[27] As in synthesis of hirsutene,[3] the linear triquinane is produced from a tandem sequence. The initial one-electron reduction of aldehyde 36, followed by the addition of the "ketyl" radical to a non-activated olefin and finally onto a acetylene was established to be a free radical process, even requiring less than two equivalents of $SmI_2$. Clearly, $SmI_2$ and TBTH may engage in several similar reactions but they operate by different mechanisms.




36

37

38

Scheme 1-10

A large number of intramolecular free radical C-C bond forming reactions, as in Scheme 1-10, involve a cyclization onto an unsaturated center. This is generally achieved by tethering a free radical precursor to an unsaturated unit (the free radical acceptor), as shown in Scheme 1-11.


**39** **40**

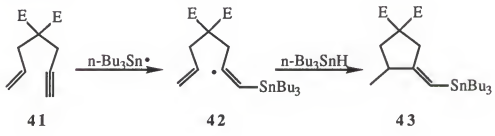
A = carbon, oxygen
B = carbon, nitrogen, oxygen
Reagents: $SmI_2$, n-BuSnH

Scheme 1-11

This dissertation will examine these cyclizations with tributyltin hydride and samarium diiodide, via the closure of the pendant free radical acceptor (39) to produce a functionalized cyclopentane ring (40). The carbon centered free radical itself may be generated from a variety of precursors, such as halides, olefins, acetylenes, or carbonyls, and react with a whole variety of acceptors, such as acetylenes, olefins, or carbonyls.

It has been known for some time that acetylenes can serve as both a free radical acceptor or as a free radical precursor. Leusink and others[16] established that in the hydrostannation reaction, shown in Scheme 1-6, a molecule of TBTH adds across a triple bond to afford 23. As shown in Scheme 1-12, the initial vinyl alkyl stannane radical (42) can also undergo intramolecular reactions; Stork and Mook demonstrated that it can be captured by a pendant acetylene or olefin (41) to form substituted

cyclopentanoid products (43).[28] An exocyclic bond forming process ensues and this reaction can serve as an alternative to the classical methods of preparation of the vinyl radical.[29]




41 42 43

Scheme 1-12

Thus, TBTH can be used to form a carbon centered radical through the initial addition of the tributyltin radical to the less hindered terminus of the acetylene. Additionally, a acetylene can act as an acceptor. As shown previously in Schemes 1-1 and 1-10, the carbon centered radical easily cyclizes with the pendant acetylene to produce triquinanes. Thus, an acetylene is a very versatile unit, functioning both as an acceptor and as a precursor in free radical reactions.

In a similar manner, olefins may also serve as electron acceptors, or as precursors, or simultaneously as both as shown in Schemes 1-1 and 1-10. The use of the nonactivated olefin, however, is not limited to the role of "middle man" in a tandem sequence. There are hundreds of examples of simple cyclizations onto nonactivated olefins[2] such as the one depicted in Scheme 1-13. In this example, the methyl substituted carbohydrate pyranoside 45 was obtained from the starting iodide 44 in an excellent yield.[30]


94%; isomer ratio: 3:1

**44** **45**

Scheme 1-13

The rate of such intramolecular cyclizations may be relatively slow compared to hydrogen atom abstraction and, as a caveat, the radical may be "quenched" or reduced before it has had time to cyclize. In many cases, the Thorpe-Ingold effect[31] (observed in the hirsutene synthesis in Scheme 1-1) may help to achieve maximum yields of cyclic products with unactivated alkenes. Most olefins used in cyclization reactions, however, possess some type of activating group like an electron withdrawing substituent to promote cyclization (Scheme 1-14).[2]


**46** **47**

EWG = $CO_2Me$, CN, Ph

Scheme 1-14

This can be explained by either valence bond theory or molecular orbital theory. Valence bond theory suggests that a resonance stabilized radical is produced after the initial cyclization.[1] Molecular orbital theory, as

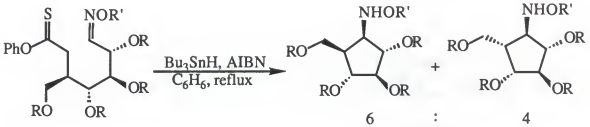
previously mentioned, suggests that the electron withdrawing group lowers the energy of the LUMO so that a more favorable interaction between the orbitals can result.[2(a)] A favorable frontier molecular orbital (FMO) interaction leads to an increase in the reaction rate and consequently a higher yield of cyclic product.[1] It is evident from the above examples, though, that in some radical cyclizations, electron withdrawing substituents are not necessary for success; this phenomenon appears to be substrate and reagent specific and will be discussed in Chapter 3.

It has also been demonstrated that the π–systems of carbonyls and oximes can act as free radical acceptors, and that carbonyls can also act as radical donors.[2] It was once believed that the carbonyl bond was too strong to undergo addition with free radicals.[2(a)] However, a surprising report by Fraser-Reid et al.[32] indicated that carbonyls are not only excellent acceptors, but also that the addition of an electron rich carbon centered radical to the electron poor site (carbon) of a carbonyl is not reversible. He also showed that the radical cyclization onto aldehydes can compete favorably with the ring closure of a 5-hexenyl radical. Tsang and Fraser-Reid[33] demonstrated this result (Scheme 15) in the addition of a pendant radical 48 onto an aldehyde in exclusive preference to an olefin in the synthesis of cycloalkanol 49.


**48** **49**

Scheme 1-15

Additionally, Corey and Pyne[34] were the first to show the addition of a radical to an oxime ether, and until studies by Hart and Bartlett and their coworkers, this work had been largely ignored.[35] Hart et al.[35(a)] studied the effectiveness of intermolecular couping of radicals and oxime ethers, while Bartlett et al.[35(b)] focused on the effectiveness of radical addition to an oxime ether using protected sugars (Scheme 1-16).

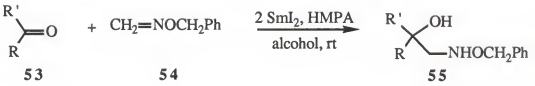



**50** **51** **52**

R = $CH_2Ph$
R' = Me or $CH_2Ph$

Scheme 1-16

These two studies demonstrated that a radical generated by functional group abstraction easily cyclized onto the oxime ether, and that the free radical reaction was not affected by other functional groups in the molecule. Further, recent publications confirm the earlier result of Corey and Pyne[34] that the oxime ether can be coupled with a carbonyl to give amino alcohols in excellent yields. Hanamoto and Inanaga[36] showed that $SmI_2$ effectively couples ketone 53 to O-benzyl formaldoxime (54) (Scheme 1-17). The process is believed to involve free radicals with $SmI_2$-promoted ketyl radical addition to the carbon of the oxime ether bond.




53 54 55

R, R' = H, alkyl

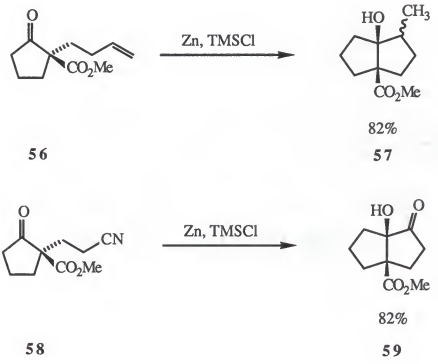
Scheme 1-17

In another report, Shono et al.[38] presented that the same coupling with carbonyls and O-methyl keto- and aldo-oximes could be achieved through an electroreductive (free radical) process. It is now widely accepted that the carbonyl and the oxime ether can function as radical acceptors.

It is also well-established that the carbonyl can function as a free radical precursor. As demonstrated in Schemes 1-5, 1-7, and 1-8, carbonyl moieties are readily reduced by the free radical reactions of TBTH and $SmI_2$. These reagents exhibit "Lewis acid-like" properties,[10, 17] and prefer to initially interact with the electron rich site (oxygen) of the carbonyl bond to form metal "ketyls" which can subsequently add to free radical acceptors.

As early as 1978, the coupling of ketones and olefins was used as a method to generate cycloalkanols. Electroreductive coupling of ketones was performed by Shono et al.[39] with moderate yields. Other studies, including photochemical[40(a)] and electrochemical methods,[40(b-e)] have confirmed the usefulness of this reaction. Additionally, Corey and Pyne[34] reported on a new method which involved the free radical generation from ketones by zinc-trimethylchlorosilane followed by the addition to a $\pi$-bond. The cyclization proceeded smoothly even with a variety of electron

acceptors including nonactivated olefin 56 and nitrile 58 (Scheme 1-18). Enholm and Prasad demonstrated that the free radical intermediate ketyl of TBTH[41] and $SmI_2$[22] also easily cyclizes. In these instances, however, an activated olefin was necessary to achieve good yields.




Scheme 1-18

This dissertation investigated the free radical behavior of the above precursors and acceptors in cyclization reactions. TBTH and $SmI_2$ were used to form radicals from alkyne, alkene, aldehyde, ketone, and enone precursors. These unsaturated centers were tethered to a variety of acceptors, including oxime ethers, α,β-unsaturated esters, styrene functions and unactivated olefins. Various combinations of the above free radical precursors and acceptors were examined in an attempt to further understand the synthetic utility of free radicals.

Chapter 2 initiated these studies with the examination of the intramolecular coupling of oxime ethers and acetylenes. In these cases, an acetylene was the free radical precursor and an oxime ether was the acceptor. The hydrostannylation reaction was utilized to afford a vinyl radical which cyclized onto a pendant oxime ether to yield a functionalized cyclopentane ring with an exocyclic methylene functionality and a protected amino group. This was the first study to combine the unsaturated functionalities of an acetylene and an oxime ether and has applicability in natural product synthesis.

Chapter 3 of this dissertation investigated the intramolecular coupling of carbonyls to $\alpha,\beta$-unsaturated esters and styrene systems. It is well established that the $\pi$-system of a carbonyl can function as a free radical acceptor and as a radical precursor. Our seminal investigations indicated that the tin "ketyl," which is formed when the tin radical adds to the oxygen of a carbonyl, easily cyclizes onto activated olefins. It was not known, however, whether the radical formed from the first cyclization could participate in additional ring forming reactions. Thus, the objective was to investigate the use of the "ketyl" reaction in tandem cyclizations. Various starting substrates, which contained either an aldehyde or a ketone, an activated olefin and a nonactivated olefin were designed in order to produce the common ring systems of fused, spiro, and joined if the reaction was successful. The yields of the systems which did undergo the tandem cyclization were generally good, and resulted in substituted products.

In chapter 4, a comparison of the tin ketyl cyclizations and samarium ketyl cyclizations was made. This is the first study to compare the two metal ketyl methods. The reactions of TBTH and $SmI_2$ are similar in that

they both initially promote one electron cyclizations to form five-membered rings. However, the similarity between these two may end there. The substrates which were subjected to the TBTH reaction conditions were also subjected to the reaction of $SmI_2$ under various conditions. In many cases, very striking results were observed. The primary focus will be on the differences between these two reagents in synthetic construction methodologies.

The use of free radicals, once thought to be unruly and relegated to simple polymer chemistry, has now expanded into the world of synthetic methodology. This has allowed chemists to synthesize complex poly-cyclic compounds, such as hirsutene and hypnophilin, from simple mono-cyclic starting materials. Complex transformations, which could not be achieved by conventional chemistry, can now be achieved in a single reaction. In all of these transformations, the key steps are the generation of the free radical from various functionalities and subsequent cyclization onto a compatible free radical acceptor. It is interesting to note that by simply varying the types of acceptors and precursors and their relative positioning within the starting substrate, a wide variety products can be obtained. Two reagents, tributyltin hydride and samarium diiodide, can initiate these free radical reactions, and although they function by completely different mechanisms, they perform similar transformations. A survey of the literature suggests that tributyltin hydride and samarium diiodide can accomplish useful, high yielding transformations under relatively mild conditions. Our work attempts to broaden the knowledge in these areas, and to contribute to the ever expanding world of free radicals in synthesis.

## CHAPTER 2

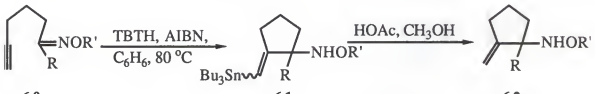
## COUPLING OF TERMINAL ALKYNES WITH OXIME ETHERS

There are only a few examples of radical cyclizations with oxime ethers. Corey and Pyne[34] originally demonstrated that an oxime ether could in fact function as a free radical acceptor, and later work by Hart and coworkers[35(a)] and Bartlett and coworkers[35(b)] confirmed its effectiveness in other cyclization and coupling reactions. Additional studies by Hanamoto and Inanaga[36] and Shono et al.[38] were performed after the publication of this research[42] and mirror Corey and Pyne's original preparation[34] of amino cycloalkanols. But, up to this point, it appeared that the use of the oxime ether was rather limited in that unsaturated precursors were never utilized in these free radical coupling reactions. We wondered if a vinyl radical would be as effective in coupling reactions as the other radicals. We envisioned the study in Scheme 2-1 in which the vinyl radical would be generated from the addition of tributyltin radical to the terminus of an acetylene,[16, 28] and could intramolecularly add to an oxime ether to yield an amino cyclopentane.

The presence of amino cyclopentanoids in natural products has spurned much interest among synthetic chemists. Many of these compounds are highly functionalized and most are interesting from both a medicinal and synthetic point of view. There are a few classical methods for synthesizing amino containing compounds such as the Gabriel preparation[43] or simple reduction of imines by lithium aluminum hydride and sodium borohydride. However, most are limited in that severe two-

electron reaction conditions are required for the transformation. A free radical generation of such a unit would permit mild conditions to be utilized, and thus other structural features in the molecule would remain intact.

This study was the first to combine a vinyl stannyl radical with the effective trapping ability of an oxime ether in a ring forming reaction. An important feature of this work, which unites the earlier work of Stork and Mook[28] with the recent findings of Hart et al.[35(a)] and Bartlett et al.,[35(b)] is that functionalized cyclic products are formed from simple acyclic starting materials. The simplest version of this process, shown in Scheme 2-1, involves the intramolecular coupling of a terminal alkyne tethered to an oxime ether (60) promoted by the hydrostannation-type reaction of tributyltin hydride (TBTH) under free radical conditions to give the hydrostannated intermediate 61.




**60** **61** **62**
56-90%

R = Alkyl, H
R' = $CH_2Ph$

Scheme 2-1

Subsequent protodestannylation[44] of 61 yields the substituted cyclopentane ring 62 with an exocyclic-methylene functionality and a protected α-amino group.[45] In order to study the scope and limitations of this coupling reaction, several systems which included the 5-exo mode and the 6-exo

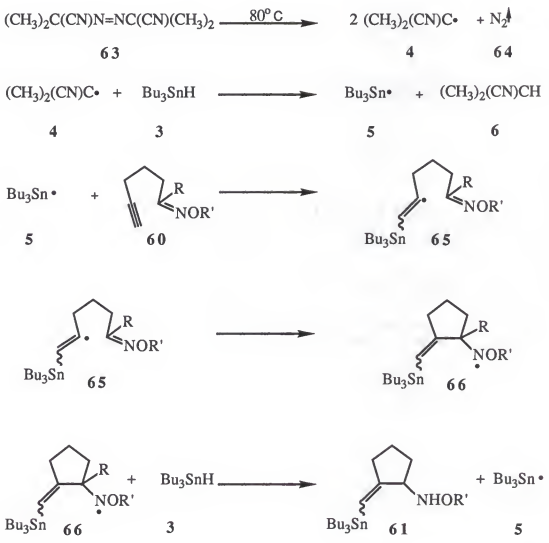
mode of cyclization with cyclic and acyclic keto and aldo oximes were examined.

In a typical experiment, the oxime ether was dissolved in dilute benzene (0.02 M) and a catalytic amount of azobisisobutylnitrile (0.02 eq) and tributyltin hydride (1.20 eq) was added. After degassing the solution with a stream of argon for 30 minutes, the reaction was heated to 80 °C for 18-24 hours. After removing the solvent under reduced pressure, the residue was subjected directly to protodestannylation and then purified by chromatography. The hydrostannated intermediate, however, could in some cases be isolated by column chromatography and is stable. The yields in these reactions were generally good, ranging from 56 to 90%. The majority of these reactions proceeded smoothly to give well-functionalized cyclic products.

The proposed radical chain mechanism begins with the thermal generation of the radical 4 in the initiation step, followed by the generation of tributyltin radical (5) by hydrogen atom abstraction (Scheme 2-2). Radical 5 then adds to the terminus of acetylene 60 and generates a vinyl radical alpha to the tributyltin moiety (65). Addition of the radical to the oxime ether at the $sp^2$ carbon affords nitrogen centered radical 66 and subsequent hydrogen atom abstraction from another molecule of tributyltin hydride, generates the final product 61 as an inconsequential mixture of isomers and yet another tributyltin radical (5) to continue the chain process.

Although not demonstrated in this study, vinyl stannanes, such as intermediate 61, are useful precursors to a variety of synthetically valuable functionalities.[10] The reactions of vinyl stannanes are too numerous to list, however a few examples are given to illustrate the potential of this

subunit in synthesis. Vinyl lithium species, for instance, can be obtained through the transmetallation reaction, which is an excellent alternative to the classical preparation of vinyl lithium compounds.[46] Cooke reported on the use of a vinyl stannane as an important intermediate in the synthesis of the defensive substance of *L. longpipes*.[47]




R = Alkyl, H
R' = $CH_2Ph$

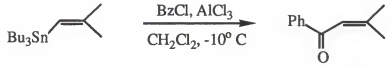
Scheme 2-2

The vinyl stannane 67 was simply treated with n-butyl lithium to give the vinyl lithium 68 (Scheme 2-3).


67 68

Scheme 2-3

Vinyl stannanes can also be used to synthesize α,β-unsaturated ketones, or enones (Scheme 2-4).[48] The vinyl stannane 69 was treated with an acid halide and a Lewis acid to give the ketone 70.



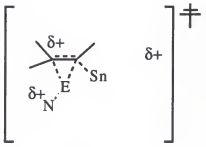

69 70

Scheme 2-4

Additionally, vinylstannanes can be successfully alkylated with α-halo esters[48] or halogenated by molecular iodine or bromine.[49] The majority of reactions of vinyl stannanes occur with retention of configuration,[44] and the yields are generally good. Thus, the vinylstannane unit can be further elaborated in order to access a variety of functional groups.

In this investigation, the vinyl stannane 61 was treated under typical acidic protodestannylation conditions to obtain the unsubstituted alkene product 62, as shown in Scheme 2-1. According to the work of Baekilmans et al.,[50] the transformation, mechanistically described as a $S_E2$, proceeds through an open transition state (Figure 2-1), with the

proton (or the electrophile) adding to the α-carbon. Cochran et al.[44] found that the solvent may actually participate in this transition state, and this confirms the early reports that bimolecular electrophilic (E) substitution for tin at a vinylic carbon takes place with retention of configuration.



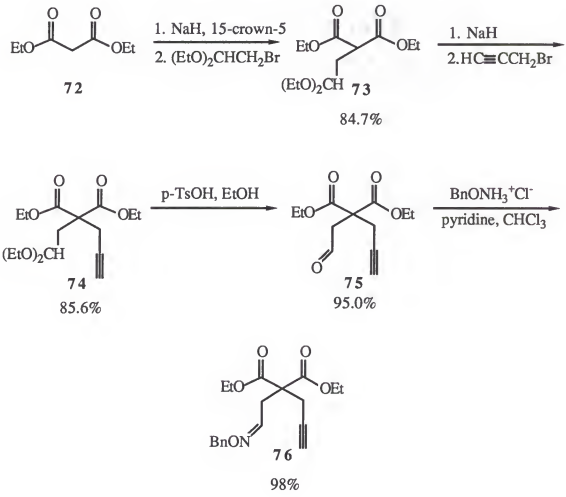

**71**

Figure 2-1

Transition state

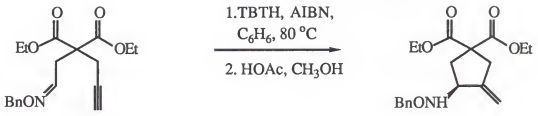
In the initial example, shown in Scheme 2-5, the aldo-oxime in 76 was tethered to an alkyne through a malonic ester backbone. The synthesis of this first reactant (76) was attempted many times in a series of reactions with the sodium salt of diethyl malonate and oxirane, ethyl formate, and chloroacetaldehyde dimethyl acetal. These experiments however, were futile and yielded only unreacted starting material. It was assumed that the anionic stabilization from the two ester groups lowered the reactivity of the diethyl malonate nucleophile. This was combined with low reactivity of many 2-carbon electrophiles which meant that the desired compound could only be successfully synthesized if stronger reaction conditions were employed. Reactant 76 was finally successfully synthesized after reacting the sodium salt of diethylmalonate (72) with bromoacetaldeyde diethyl

acetal and 15-crown-5 (specific for sodium cations) under concentrated conditions in refluxing toluene for two days. Protected aldehyde 73 was then smoothly alkylated with propargyl bromide to yield the alkyne 74. Subsequent treatment of the acetal with dilute p-toluene sulfonic acid afforded simple aldehyde 75. Finally, the aldehyde was treated with O-hydroxybenzyl amine hydrochloride in chloroform and produced oxime ether 76 in a 60% overall yield for 4 steps.




Scheme 2-5

In a cyclization reaction, shown in Scheme 2-6, a mixture of the syn- and anti-oxime ethers 76 were subjected to standard free radical conditions with tributyltin hydride, followed by the typical destannylation conditions of acetic acid in methylene chloride to give a single substituted cyclic product 77 in 56% yield. No other identifiable products were isolated from the reaction. Thus, a highly substituted cyclopentene was formed from a simple straight chain substrate.

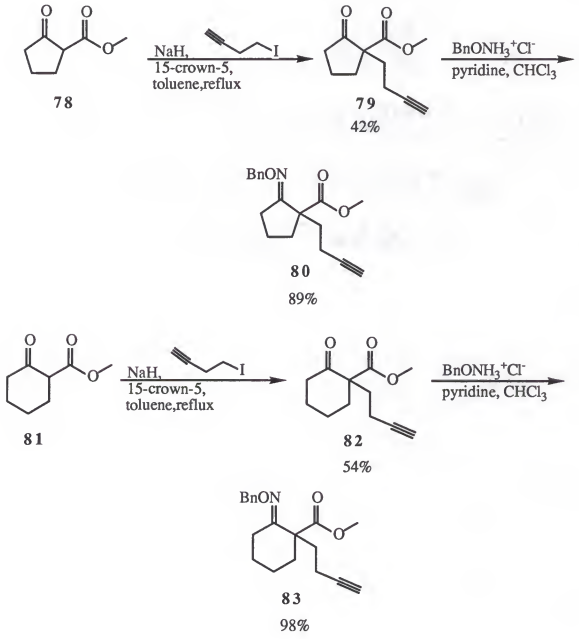



**76** **77**
56%

Scheme 2-6

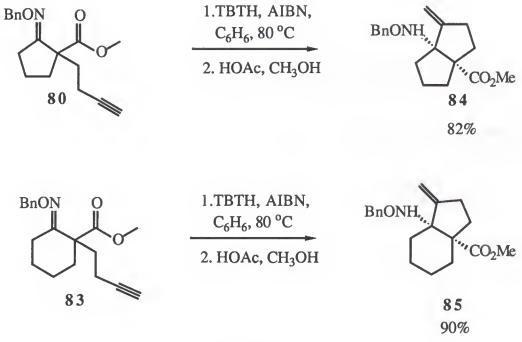
The next two cases exploited cyclic keto-oximes bearing a pendant alkyne unit and demonstrate the effectiveness of this reaction in the synthesis of bicyclo[3.3.0]- and bicyclo[4.3.0.]-fused ring systems. Once again the malonic ester synthesis and analogous β-dicarbonyl alkylations proved to be invaluable methods for obtaining the various nonvolatile starting substrates, as shown in Scheme 2-7. One major problem, however, was the apparent lack of reactivity of the electrophile, 4-iodobutyne, which was used in the synthesis of the starting substrates. This problem was remedied by substituting toluene for tetrahydrofuran, which would allow higher reaction temperatures to be obtained, and using a crown ether. Keto-alkynes 79 and 82 were both prepared by direct

alkylation of the cyclic keto-esters with 4-iodobutyne, in 42%, and 54% yields, respectively. The oxime ethers 80 and 83 were next both formed from conditions using O-benzylhydroxylamine hydrochloride and pyridine.



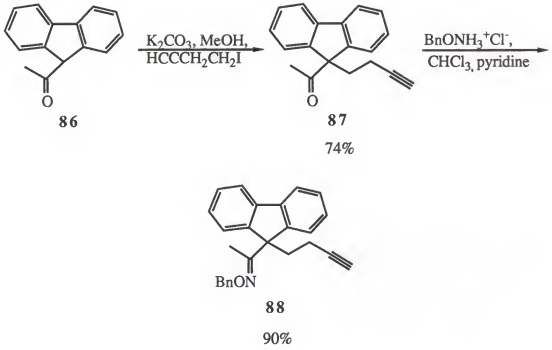

Scheme 2-7

In both the 5-membered and 6-membered ring cases, the anti-oxime ethers 80 and 83 were subjected to the hydrostannylation and destannylation reactions and both smoothly generated single functionalized bicyclic products in 82 and 90% yields, respectively, as shown in Scheme 2-8. It should be noted that the ester functionality in these cases did not adversely affect the reaction and remained intact throughout hydrostannation and destannylation. The hydrostannation-cyclization sequence in these two examples established a new route to biologically active fused ring systems.




Scheme 2-8

As an outgrowth of the above research, a novel method to generate spiro ring systems was examined (Scheme 2-9). Thus, 9-acetylfluorene (86) was alkylated with 4-iodobutyne (74%) and then alkyne 87 was treated with O-benzylhydroxylamine hydrochloride to afford the oxime ether 88 in 90% yield.

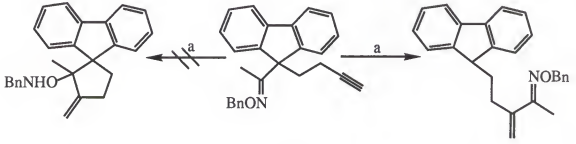



**86** **87** 74%

**88** 90%

Scheme 2-9

When subjected to standard free radical conditions, however, this oxime ether (88) did not form the expected spiro-ring system (89) as shown in Scheme 2-10. Instead, a single keto-oxime ether product 90, very different from the starting oxime ether, was isolated in 58 % yield from the reaction.

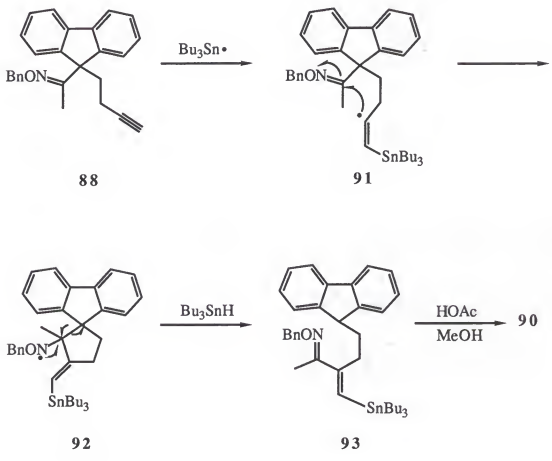



**89** **88** **90** 58%

KEY: a) 1.TBTH, AIBN, $C_6H_6$, 80° C ; 2. HOAc, $CH_3OH$

Scheme 2-10

A plausible mechanistic explanation for the formation of this rearranged keto-oxime (Scheme 2-11) emanates from the initial formation of vinyl tin radical intermediate 91 by the addition of tributyltin radical to the terminal acetylene.

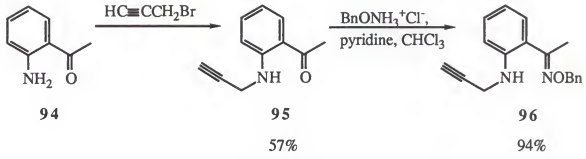



Scheme 2-11

A subsequent cyclization with the $sp^2$ carbon of the oxime ether affords the nitrogen-centered free radical species 92. After undergoing ring cleavage to produce the fluorene-stabilized radical, a transfer of hydrogen radical from tributyltin hydride renders the ring-opened oxime ether 93. Since none of the other cases resulted in a similar bond cleavage reaction, it

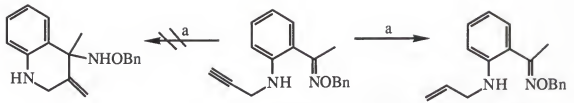
appears that the driving force of this rearrangement relies on the superior radical-stabilizing effect of the fluorene ring system. The product formed in this reaction lends support to the argument that the ring did initially form; however, it appears that the hydrostannation-cyclization reaction is not well suited for systems that may a undergo a facile beta-scission rearrangement to form more stable radical species.

The final example in these studies was an unsuccessful attempt to apply the cyclization reaction to the formation of 6-membered rings. Substrate 96 was synthesized from a series of reactions commencing with reaction of propargyl bromide with 2-aminoacetophenone (94) to produce the keto-alkyne 95 in 57% yield, shown in Scheme 2-12.




Scheme 2-12

Keto-alkyne 95 was subsequently treated with O-benzylhydroxylamine hydrochloride in methylene chloride to yield oxime-alkyne 96. We had hoped that cyclization of 96 would have provided a new route to disubstituted aniline compounds such as 97, shown in Scheme 2-13. However, 96 failed to cyclize and a simple alkene 98 was the only observed product in 60% yield after hydrostannation and subsequent destannylation.




97 96 98

60%

KEY: a) 1.TBTH, AIBN, $C_6H_6$, reflux; 2. HOAc, $CH_2Cl_2$

Scheme 2-13

There are several mechanistic explanations for the apparent failure of the vinyl tributyl tin radical to cyclize in this last case. The most obvious of these is that the 6-exo radical cyclizations are slow relative to the rate of hydrogen atom abstraction. This has been documented by Beckwith, who showed that the rate of 5-hexenyl exo-cyclization is about 33 times faster than that of 6-heptenyl cyclization at 65 $^oC$[6(a)] (Table 2-1).

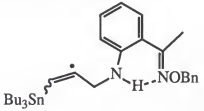
Table 2-1

**Rates of Exo-Cyclization**

| Radical | $k_{exo}(s^{-1})$ |
|---|---|
| 5-hexenyl | $3.6 \times 10^5$ |
| 6-heptenyl | $1.1 \times 10^4$ |

This decrease in reactivity increases the "window" of radical lifetime, and allows more time for the radical to engage in undesired destructive chain-termination steps,[2(c)] or hydrogen atom transfer, before cyclization has occurred. The second and perhaps more germane explanation involves the stereochemistry of the starting substrate. Resonance in the aniline ring imparts some degree of $sp^2$ character onto the nitrogen, and thus the

rotation around the nitrogen-carbon bond would be slowed. Rotation is also hindered by hydrogen bonding within oxime ether 99 (Figure 2-2). Thus, the rotation about the aryl nitrogen bond is restricted and the pendant alkyne unit is secured away from the oxime, unable to achieve effective orbital overlap for the cyclization reaction.




**99**

Figure 2-2

Hydrogen bonding

These explanations show that it is difficult for the vinyl radical 99 to cyclize onto the oxime ether and simple hydrostannation results. Without additional experimental data, however, it is difficult to confirm these mechanistic rationals. A combination of the rate of cyclization and molecular geometry appear to play important roles herein. In any case, the rate of hydrogen atom donation to this compound is much greater than cyclization, and simple alkene 98 was the only isolated product. Finally, it should be noted that there are too many confounding variables involved in this 6-ring substrate to completely rule out six membered ring cyclizations of this type.

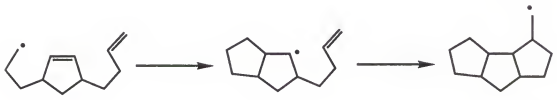
In conclusion, the intramolecular coupling of oxime ethers to terminal alkynes can be applied to the synthesis of substituted simple and fused ring systems. The application of this methodology to aromatic

systems, such as the two described in this dissertation, is questionable. The possibility of the β-scission process described earlier is one noted difficulty (Scheme 2-11). It is apparent though, that the initial coupling of the oxime ether and the alkyne in this case worked. The only system which failed to cyclize, in fact, was in an example in which it appears that molecular geometry and cyclization rate prohibited ring closure. Nevertheless, this reaction does appear to be a viable and practical method for the synthesis natural products.

## CHAPTER 3

## TANDEM COUPLING OF CARBONYLS WITH ALKENES

Tandem radical cyclization, which is the formation of two or more consecutive rings from one initial alkyl radical, has become a popular method to generate the complex ring systems of natural products.[2,3,27] The mechanism of ring formation (Scheme 3-1) is analogous to a relay race, where each runner hands off the baton to the next, and so on. In this comparison, the baton is likened to the free radical as it "travels" from one newly formed ring to the next. As previously demonstrated in the hirsutene[3] and hypnophilin[27] synthesis, radical intermediate 100 is first captured by an internal olefin-generating radical 101, which is then finally entrapped by another olefin, or acetylene yielding 102.

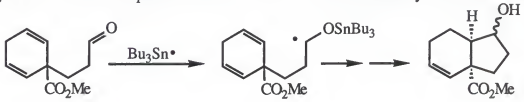


**100** **101** **102**

Scheme 3-1

In each case, the "cascading" radical has generated three sequential rings from a monocyclic substrate. This reaction is not only well suited for the synthesis of the linearly fused triquinanes, such as hirsutene and hypnophilin, it can also be used to generate other ring systems, and there is a great desire to among chemists to see how many sequential rings can be formed from one original radical.

The original radical, as previously demonstrated, may be generated from a variety of precursors; this research focused specifically on tin-ketyl induced tandem cyclizations. As previously described in Chapter 1, a tin ketyl is formed from the addition of tributyltin radical to a carbonyl moiety.[15] This so called (stannyloxy)alkyl radical, or O-stannyl ketyl, was originally described by Tanner et al.,[51] and later by Beckwith and Roberts[52] in the synthesis of bi- and tri-cyclic systems. As shown in Scheme 3-2, Beckwith and Roberts demonstrated that aldehyde 103 cyclizes to give a mixture of epimeric alcohols 105 in an excellent yield of 90%.



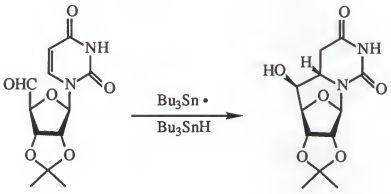

**103** **104** **105**

Scheme 3-2

However, they noted that the reaction, was very "sluggish," and, in fact, required additional amounts initiator and TBTH in order to go to completion. Beckwith speculated that the formation of the (stannyloxy)-alkyl radical, which we refer to as a tin ketyl, may be reversible, or that the rate of the radical's initial formation or its subsequent cyclization was very slow.[52]

More recent research indicates that the ketyl cyclization is effective in most cases and has potential applicability in synthesis. Sugawara et al.[53] used the tin ketyl in the cyclizations of nucleosides (Scheme 3-3). In this example, the ketyl radical of 2', 3'-O-isopropylideneuridine 5'-aldehyde (106) cyclizes onto the activated olefin in the uridine ring system to form carbon-bridged cyclonucleoside 107. Note that in this example a

six membered ring is formed. Sugawara et al. also found that this procedure was effective, though to a lesser degree, with purine nucleoside 5'-aldehydes.

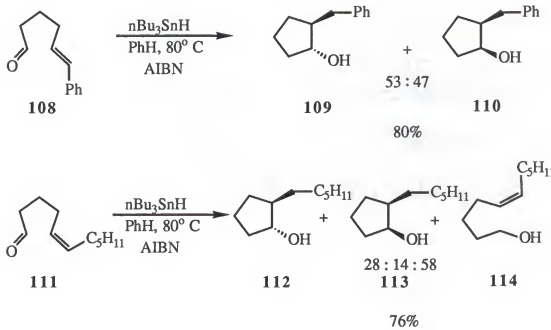



**106** **107**

Scheme 3-3

Other than these three isolated examples, little systematic work has been done to study this cyclization. In the first study to examine the scope and limitations of this alkene/carbonyl coupling, Enholm and Prasad[41] showed that the tin ketyl was effective in cyclizations of both aldehydes and ketones (Scheme 3-4). In this work, activated (electron deficient) and nonactivated olefins were compared under standard free radical conditions. They found that an activated olefin such as the styrene unit in 108 was an important prerequisite for successful cyclization, and although cyclization of the nonactivated olefin (111) did occur, the predominant product was the simple acyclic alcohol 114. It is apparent from this example that the stannyl ketyl radical did not immediately cyclize and was subsequently reduced by another molecule TBTH. Thus, the rate of cyclization is slow with nonactivated olefins and competes with the rate of hydrogen atom

abstraction from TBTH. This result appears to support the early hypothesis of Beckwith and Roberts,[52] that the cyclizations O-stannyl ketyls may be slow.




Scheme 3-4

The apparent lack of reactivity of some tin ketyls to nonactivated olefins can be related to the nucleophilicity of the ketyl species. Nucleophilic radicals, or electron rich radicals with high lying SOMOs, preferentially interact with the LUMOs of electron-poor olefins, as discussed in Figure 1-1 in Chapter 1.[2] With ketyls, the alkoxylate anion imparts some negative character onto the radical, thus making the radical more nucleophilic than a simple carbon centered radical. By using ESR techniques, Mile[54] verified this effect in sodium ketyl species. The carbon of this ketyl bears 70% the of unpaired electron density. This reduction in the unpaired electron density at the carbonyl carbon is associated with a comparable increase of unpaired electron density at the oxygen atom.

Thus, the resonance contribution of 116 (Scheme 3-5) is minor, yet very important, and indicates that some anionic character is imparted onto the carbon.

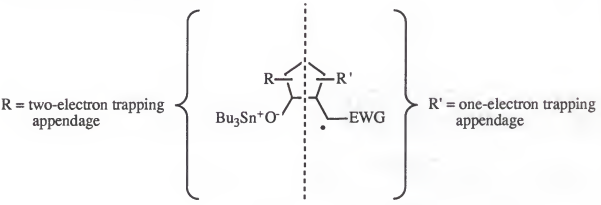

Scheme 3-5

Although the contribution of this resonance structure 116 is believed to be smaller with M+ equal to $Bu_3Sn$ than when M+ is equal to Na, it may be significant enough to raise the SOMO energy of the free radical.[2(b)] Nevertheless, it should be mentioned that there are a lot of examples of ketyl cyclizations onto nonactivated olefins;[2] this phenomenon may simply be substrate specific.

Enholm and Kinter[55] have taken the tin-ketyl radical a step further by creating tin-ketyl enolates. In this work, α,β-unsaturated ketones were reduced by the tributyltin radical to give tin-ketyl enolates. In each case, the free radical on the β-carbon (instead of the actual tin ketyl radical) cyclized onto the activated olefin to give trans products. It is expected that once the tin enolate has cyclized it can undergo additional ring forming reactions to form more complex products. From this research, and those of others, it appears as if the tin ketyl species is very versatile, yet behaves like a slow-reacting simple carbon centered free radical.

In all of the previous research in the area of tin ketyls, the radical formed from the addition of the tin ketyl to an olefin was simply reduced by TBTH to yield a substituted cyclic product. The initially cyclized

radical anion species 117 (Figure 3-1), however, exhibits a special dichotomy of reactivity which was not fully exploited by other researchers and merited additional study.




**117**

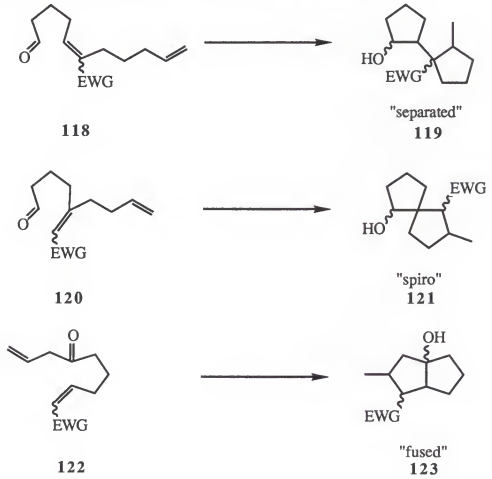
Figure 3-1

One electron versus two electron reactivity

The left hand side of this radical species should exhibit a two electron manifold of reactivity (anionic) and the right hand side should posses one electron capability (free radical). We envisioned intramolecular "traps," such as π-bonds, which would capture either or both the free radical or the anion (Michael) in order to form complex ring systems in a tandem fashion. Although the dotted line separates the halves of intermediate 117, this barrier is not absolute; potential sites for the appendage R or R' can exist at any position, including intermolecular radical traps. This research focuses specifically on the R' or one-electron sequential reactions of this intermediate species.

The purpose of this study was to investigate the application of tin ketyls in tandem cyclizations using various free radical precursors and acceptors, which contained either an aldehyde or ketone, and an activated

olefin and a nonactivated olefin. An activated olefin, as it is referred to by free radical chemists, is an olefin which possesses some type of electron withdrawing substituent such as an ester or phenyl group, which also functions to stabilize the radical by resonance delocalization and reacts via the HOMO.[2(a)] By simply varying the position of a nonactivated olefin tether in the molecule a wide variety of substrates were envisioned. These compounds were designed to generate the common ring systems of "separated," 119, "spiro," 121, and "fused," 123, if the reaction was successful (Scheme 3-6). Additionally, the activating capacity of styrene, a rarely studied radical acceptor,[56] and α,β-unsaturated esters were investigated as EWGs (electron withdrawing groups).



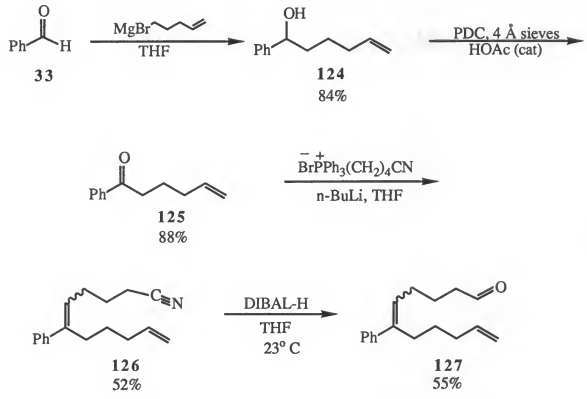

Scheme 3-6

In a typical experiment, the olefin was dissolved in dilute benzene and a excess of TBTH (2-4 equivalents) and a catalytic amount of AIBN (0.1-0.2 equivalents) were added. The mixture was degassed with argon and then heated at 80 °C for 18-24 hours. Monitoring the reaction by thin layer chromatography elucidated the extent of reaction completion. Some substrates required additional amounts of AIBN, as well as TBTH, to initiate reduction and the ease of the reduction-cyclization varied markedly from substrate to substrate. In fact, some compounds were very reluctant to cyclize and the additional TBTH and AIBN only increased the number of undesirable and unidentifiable products. However, the yields of the systems which did undergo the complete tandem cyclization were generally good and resulted in the desired cyclization products.

In all of the reactions, a number of stereoisomers were isolated, and although the number of products was generally less than what was predicted, this research was not designed to investigate the stereocontrol of TBTH reactions. All of the starting substrates were racemic, and virtually void of functionalization other than that which was necessary for cyclization. Therefore, the systems were not intentionally "biased" and stereoselectivity was not expected; the focus of these studies is on the basic success or failure of the cyclization. Our initial observations from this work indicate that the complexity of the stereochemical investigations relegates those studies to later reports.

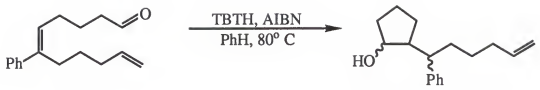
The first case examined the tandem reaction of a "separated" ring substrate (i.e. type 119). The starting substrate (Scheme 3-7) was prepared by a series of reactions, commencing with the Grignard reaction of benzaldehyde and 1-pentenylmagnesium bromide followed by an PDC oxidation to produce 1-phenyl-6-hepten-1-one (125). A unusual Wittig

reaction with iodo-triphenylphosphoniumvaleronitrile and ketone 125 gave the nitrile (126) as a 1:1 mixture of syn to anti isomers, which was subsequently reduced with DIBAL to give aldehyde 127 in an overall yield of 21%.




Scheme 3-7

This set the stage for our ketyl tandem process. Treatment of this aldehyde with an excess of TBTH (2.4 equivalents) in dilute benzene (0.04 M) (Scheme 3-8) afforded two mono-cyclic compounds (128, and 129), in approximately equal ratio in 73% yield.




**127**

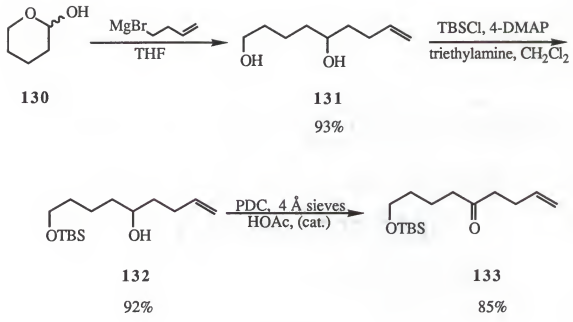
**128** high Rf isomer
**129** low Rf isomer

73%

Scheme 3-8

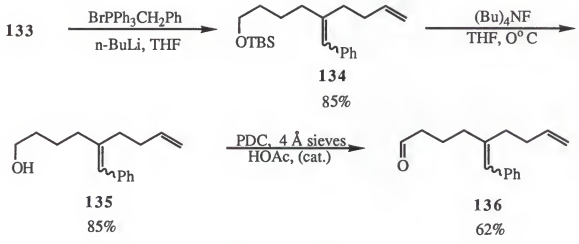
In this case, the rate of hydrogen atom abstraction from TBTH by the intermediate benzyl radical was faster than the second cyclization step, and one ring was formed. There are a few plausible mechanistic reasons for the apparent failure of the second cyclization. The intermediate tertiary benzyl radical was highly resonance delocalized and may simply have been too stable.[2] This congested radical may also have been too sterically hindered to immediately add to the olefin Because the rate of hydrogen atom abstraction from TBTH is a fast reaction, only rapid radical cyclization reactions can compete and generally, radicals that are slow to add to alkenes are easily quenched by TBTH.

In marked contrast to the example above, the "spiro" ring example (i.e. type 121) met with success. The precursor substrates were synthesized from a six-step sequence starting with the reaction of lactol 130 and 1-butenylmagnesium bromide. The primary alcohol of the resulting diol (131) was selectively protected with t-butyldimethylsilyl chloride, and the secondary alcohol was oxidized with PDC to afford the ketone 133. This ketone was used to synthesize both a styrene system and an $\alpha,\beta$-unsaturated ester, and a bifurcation in the reaction sequence was adapted.



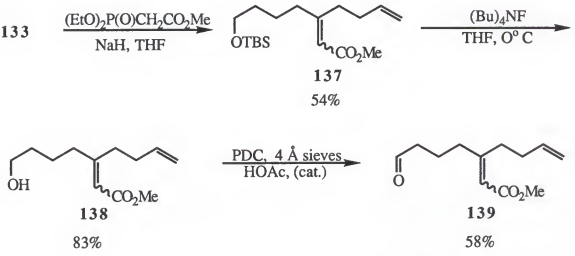

Scheme 3-9

The styrene system was synthesized by the following steps as indicated in Scheme 3-10. Ketone 133 was treated with benzylidine triphenylphosphorane under standard conditions to yield styrene 134 as a 1:1 mixture of geometric olefin isomers. The silyl protecting group was removed with tetrabutylammonium fluoride to give alcohol 135, which was subsequently oxidized with PDC to yield the aldehyde 136.




Scheme 3-10

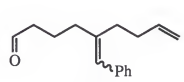
The α,β-unsaturated ester was constructed in an analogous manner from 133. The reaction of ketone 133 with methyl diethylphosphonoacetate and sodium hydride yielded the ester 137, which was deprotected to produce alcohol 138 and subsequently oxidized to give the key aldehyde (139).




Scheme 3-11

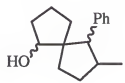
When subjected to the free radical conditions, as shown in Scheme 3-12, aldehydes 136 and 139 gave successful results. In both cases, the expected spiro-[4.4]-ring system was obtained and fewer stereoisomers (4, and 5) were formed than what was predicted (8). The styrene system (135) gave a high yield of four products (Scheme 3-12). Subsequent chromatography to isolate the individual isomers gave a ratio of 1:1:1.2:0.4 of isomers 140, 141 and 142 in 75% yield. Two of the isomers (142) had low Rf values by thin layer chromatography and could not be separated. The α,β-unsaturated system yielded five spiro products 143 and 144 in

could not be separated and were characterized as a mixture. No mono-cyclized products were observed in either reaction. This is the first example of a tin ketyl initiated spiro ring formation, and the first example of a successful tin ketyl initiated tandem cyclization.



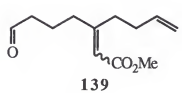

**136**

TBTH, AIBN
PhH, 80° C



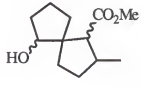

**140** high Rf isomer
**141** middle Rf isomer
**142** low Rf isomers

75%




**139**

TBTH, AIBN
PhH, 80° C



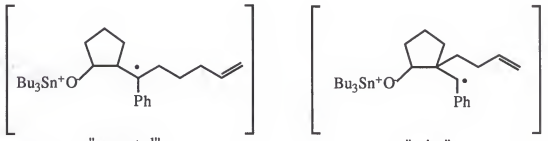

**143** high Rf isomer
**144** low Rf isomers

55%

Scheme 3-12

The difference between the successful "spiro" and unsuccessful "separated" cases is the reactivity of the intermediate radical (Figure 3-2). As described previously, the initial cyclization of the separated ring system gave a tertiary radical (145) which did not cyclize onto the pendant unactivated olefin. As discussed in Chapter 1, the Beckwith model can be used to describe the transition state of 5-hexenyl cyclizations (Scheme 1-4).[6] Generally, with these cyclizations, methyl substituents at the radical

center have very little effect on the rate of cyclization.[6] But in this case, two bulky groups (phenyl, and cyclopentyl) occupy this position and the pendant olefin may be denied steric access to the radical center, and the transition state conformation is never attained. In the "spiro" case a secondary radical (146) is formed and has little difficulty approaching the olefin. This secondary radical should also be stabilized (both are benzyl radicals) by resonance and it appears that this radical is also somewhat sterically hindered. So, both cases exhibit some steric interference; however, the tertiary radical 145 is simply more stabilized and consequently simply abstracts a hydrogen atom from TBTH.

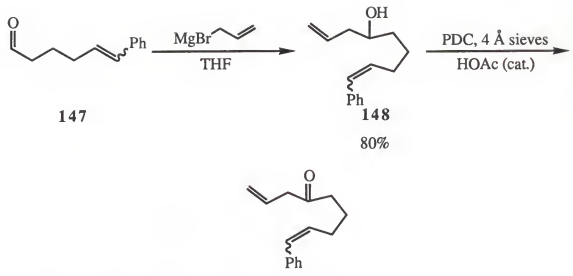



"separated" **145** "spiro" **146**

Figure 3-2

Comparison of intermediate radicals

The cyclization of the "fused" ring system (i.e. type 123) proved to be very challenging. Initially, a system which possessed a β,γ-unsaturated ketone and either a styrene unit or an α,β-unsaturated ester was envisioned. The synthesis of both precursor compounds was quite simple and this is pictorially demonstrated in Schemes 3-13 and 3-14. Aldehyde 147[57] was treated with allylmagnesium bromide to give alcohol 148. Subsequent treatment of 148 with PDC afforded the styrene ketone 149 as a 2:1 mix of geometric isomers (Scheme 3-13).

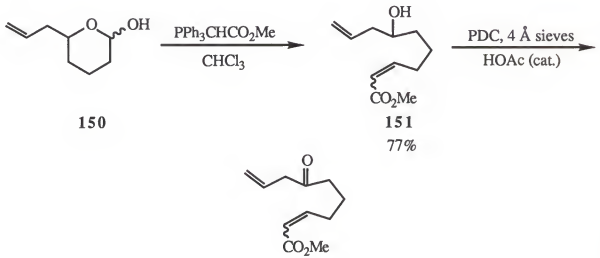



**147** **148** 80%

**149** 48%

Scheme 3-13

Lactol 150[58] was treated with methyl(triphenylphosphoranylidene)-acetate to yield the α,β-unsaturated ester. Subsequent treatment with PDC afforded the keto-ester 152.




**150** **151** 77%

**152** 70%

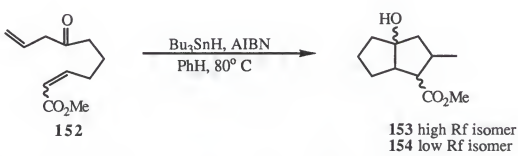
Scheme 3-14

The styrene and ester ketones were isolated in a reasonable yields (48%,and 56%, respectively) and subjected to the action of TBTH. Isolation and NMR characterization of the resulting products indicated that a substantial amount of the product from the styrene example was formed from the migration of the terminal unsaturated bond into conjugation with the ketone. Subsequent reduction by TBTH of the resulting unsaturated ketone, yielded the saturated ketone and alcohol. Double bond migration was observed in the ester stabilized case, but to a lesser degree. Because double bond migration is often attributed to the action of adventitious acids or bases, and no plausible free radical mechanism could be conceived, trace contamination in the starting materials was the suspected culprit. The glassware was then treated with trimethylsilyl chloride to reduce acidic contaminants on the glass walls of the reaction vessel.

It should be noted that 149 and 152 were subjected to the free radical reaction a number of times under a variety of conditions in an attempt to improve the yields and reduce the number of undesirable byproducts. Interestingly, the GC trace of the reaction of the 2:1 geometric mixture of the styrene system (148) under dilute conditions and with a slight excess of TBTH (1.2 equivalents) showed the predominance of the trans-styrene compound. The ring may have initially equilibrated to give the more thermodynamically stable trans isomer. Simple addition to the olefin by TBTH does occur in this example and may also be responsible for bond equilibration. Thus, the styrene case appears to be resistant to cyclization, and additional equivalents of TBTH only increased the number of unidentifiable products. It is suspected from these results that the phenyl may not be stabilizing the free radical enough to prevent the reverse reaction. Although the free radical intermediate in this case is similar to

the successful spiro example, it appears that the olefin migration, which generates an α,β-unsaturated ketone, may prevent the initial cyclization.

Ester 152, however behaved quite differently and we were relieved to obtain the fused ring system with this substrate. The reaction was sluggish, and somewhat messy. A few minor products could not be completely identified, but it was surmised that these were the products the result of double bond migration. Two major bicyclic isomers (153 and 154) were isolated in a 52% yield (Scheme 3-15). Even under a variety of conditions, this yield could not be improved. Yet, it seems from these results that the ester was a promising substrate and certainly the α,β-unsaturated moiety was better at "promoting" the initial cyclization and stabilizing the intermediate radical than the styrene system. Thus the ester lowers the energy of the LUMO further than the phenyl, and it appears to be superior in activating the olefin in these studies.




**152**

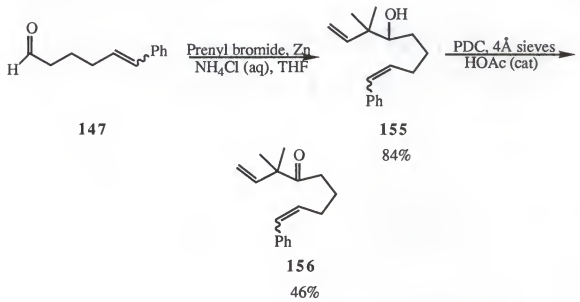
**153** high Rf isomer
**154** low Rf isomer

54%

Scheme 3-15

In order to prevent double bond migration, new systems were designed in which the olefin migration was blocked by a geminal dimethyl substituent. These systems provided interesting, and unambiguous results,

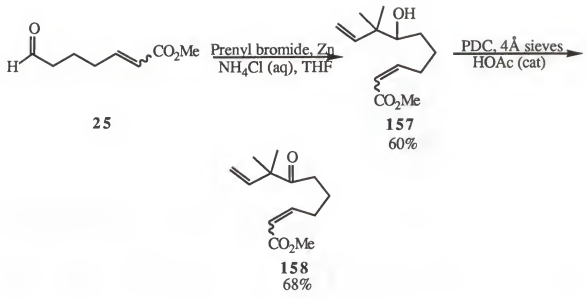
and were synthesized in a manner analogous to the above compounds (Schemes 3-16, and 3-17). The styrene system was synthesized from the reaction of aldehyde 147,[57] prenyl bromide and zinc dust[59] to give alcohol 155, which was subsequently oxidized to give the ketone 156.




Scheme 3-16

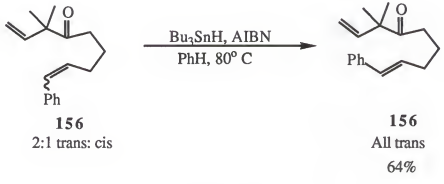
Similarly, the ester was synthesized from the reaction of prenyl bromide, zinc dust and aldehyde 25.[57] The alcohol was oxidized to give the ester ketone 158.

The behavior of styrene ketone 156 paralleled that of the original unmethylated styrene compound and under similar conditions, a 2:1 mixture of trans: cis styrene 156 gave only the trans styrene product in 64% yield (Scheme 3-18).




Scheme 3-17

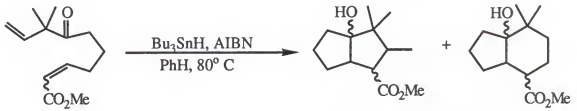
It is possible that the cis isomer may be reacting to give products which were not isolated; however, the trans isomer was the only product observed in the reaction by thin layer chromatography and GC analysis




Scheme 3-18

The ester also behaved similarly to its des-methyl counterpart (Scheme 3-19). Three products, including a bicyclic indane ring system (161) were isolated in a 50% yield (58% based on recovered starting material). The indane-ring system, which originated from a 6-endo-trig

cyclization occurred from the second cyclization because of the steric hindrance of the geminal methyls blocked 5-exo-trig cyclization. It is well established that regioselectivity in free radical reactions is governed by a number of factors, including steric hindrance.[6] It is not surprising then, the formation of this product is observed with the geminal methyl substrate.




**158**

**159** high Rf isomer
**160** low Rf isomer

58%

**161**

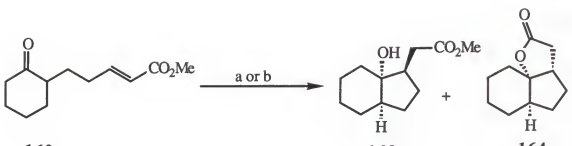
Scheme 3-19

From this research, it appears that the tin ketyl induced tandem cyclization is reasonably effective and depends markedly on the starting substrate and the activating group. The "spiro" and "fused" ring substrates smoothly cyclized to give the expected products, while the "separated" ring substrate appeared to be either too hindered or too stabilized yield the tandem product, and gave only the mono-cyclized ring system. In the "fused" ring example the difference in activating ability between the ester and phenyl groups was noted. In this case, the $\alpha,\beta$–unsaturated ester appears to be more effective than the styrene system. It is clear that the activating groups did not make a difference in the "spiro" ring example; but they functioned differently in the "fused" example.

# CHAPTER 4
# A COMPARISON OF TANDEM RING FORMATION WITH TIN AND SAMARIUM KETYLS

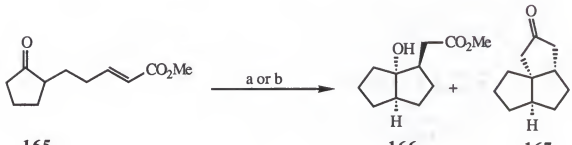
Up to this point, this dissertation has focused on the reactions of tributyltin hydride. This reagent engages in a whole host of reactions from hydrostannation to reduction, and as demonstrated in the previous chapters, it can effectively be used to couple a variety of unsaturated centers to form cyclic products. Although samarium diiodide undergoes reactions similar to tributytin hydride, these compounds have never been compared in a single study. There are separate, yet parallel, studies of these reagents, however. Investigations by Enholm and Trivellas,[22] and Enholm and Prasad[41] confirm the similarities between these two reagents. In each of these investigations (Scheme 4-1), aldehydes and ketones were coupled with olefins by the action of samarium diiodide and tributyltin hydride, respectively. With both reagents, successful cyclization occurred only in the activated olefin examples, and the yields for each method were similar. Samarium diiodide exerts a degree of stereocontrol which is not observed with the tributyltin hydride method, as evidenced by the selective formation of bicyclic alcohol 163 over lactol 164 (250 : 1); whereas only moderate selectivity was observed in the TBTH reaction (76 : 24).

But stereoselectivity is not the only difference between these two compounds. First, and foremost, they function by entirely different mechanisms. As discussed in Chapter 1, Schemes 1-2, and 1-5, TBTH is a classical free radical reagent and when subjected to an initiator it engages




**162** **163** **164**

11.5: 1 (a)
58: 42 (b)




**165** **166** **167**

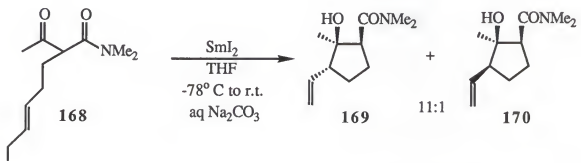
250: 1 (a)
76: 24 (b)

KEY: (a) $SmI_2$, THF, MeOH, $0^{O}$ C (b) TBTH, AIBN, Benzene, $80^{O}$ C

Scheme 4-1

in a chain radical mechanism to form products.[3] Samarium diiodide, however, is simply a very powerful one electron reductant. It "donates" an electron to the unsaturated system (Scheme 1-7),[18,19] and the samarium (II) ion is oxidized to the more stable Sm (III) state.[18(b)] Additionally, unlike the single-electron chain reactions of TBTH, the reactions of samarium diiodide usually involve a two net electron transfer because two full equivalents of samarium diiodide are necessary for the reaction completion. It is a one electron process until the first electron is reduced by another equivalent of $SmI_2$ to produce an anion.

Secondly, dihalo samarium compounds are inherently electropositive; they seek out electron donor-type ligands and non-bonded electron pairs.[19] This is obvious from the reactions of samarium diiodide; only compounds which posses some type of electron rich substituent, such as a halide, or an oxygen, engage in $SmI_2$ reactions. Tributyltin hydride, however, adds to olefins or alkynes, in the hydrostannation reaction[6] (Scheme 1-6); the initial coordination to some heteroatom is not necessary. These reactions have not been observed with $SmI_2$.[18] Furthermore, the $Sm^{+3}$ ions, which result from the oxidation of $SmI_2$, are hard acids and complex preferentially to hard bases like fluoride and oxygen.[19] These ions also have a high coordination number, and the reactions of samarium diiodide are believed to occur in the coordination sphere in which THF is also coordinated.[19] This coordination ability is advantageous because stereochemistry can be controlled through chelation. Molander et al. demonstrated this in the synthesis of cyclopentanols (Scheme 4-2).[60]




Scheme 4-2

β-Oxoamides (168) and esters provided excellent diastereoselective control (11:1) in the intramolecular coupling. In this example three stereocenters are formed, with epimerization in the vinylic unit (169, and 170). Thus, samarium diiodide possesses a high oxophilicity and can

easily coordinate with other atoms; tributyltin hydride has much less coordination ability and oxophilicity.

Thirdly, the ketyls formed from the reduction of a carbonyl by these metal compounds are different. As demonstrated in previous chapters, the ketyl species is a radical ion in which the radical is positioned on the carbon, and the anion rests on the more electronegative oxygen (Schemes 1-7,1-9, and 3-5).[51,52] Because, it has been demonstrated[54] that some of the anion character is imparted onto the adjacent radical in sodium ketyl species, the type of metal, and ultimately the strength of the polarization of the O-metal bond, must govern the nucleophilicity, or the negative character of the radical. The high ionic character of O-metal bond leads to a more electron rich oxygen and a more nucleophilic radical because the SOMO is elevated. Generally, the reactions of samarium diiodide are ionic in nature,[19] and the formation of the ketyl is no exception. However, the O-metal bonds of tin are much more covalent, but easily polarizable.[10] Thus, we believe the samarium ketyl is more nucleophilic than the tin ketyl species.

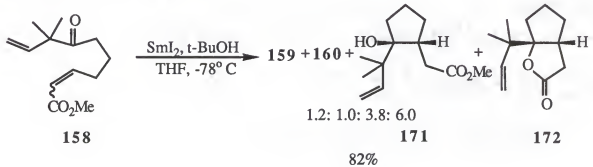
With the above differences and similarities in mind, we decided to compare the two methods in order to get a better understanding of the mechanism of $SmI_2$ reductions. A few of the compounds from the preceding chapter were selected on the basis of ease of preparation and were subjected to samarium diiodide reduction. As shown in Chapter 3, the ester stabilized olefin 158 gave a mixture of bicyclic products (Scheme 3-19), and styrene substrate 156 yielded only a trans-equilibrated product. (Scheme 3-18) under standard TBTH conditions. It was expected that the samarium reduction would give similar products; however, this was not the case. The reaction conditions were varied, and the ratio and types of

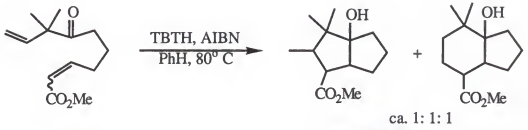
products were elucidated by GC and NMR analysis. As in Chapter 3 the stereochemistry was not studied. In these substrates, the stereochemistry was complex and a firm basis for that study will require much simpler compounds than those shown herein. However, it is noteworthy that the addition of various amounts hexamethylphosphoramide (HMPA) changed the ratio of the products, and increased the stereoselectivity of the reaction.

In a typical reaction, an excess of samarium metal was placed in a flame-dry flask under an inert atmosphere of argon and a small amount of THF was added. Methylene iodide was added to this slurry, and rapid heat evolution was observed. After a few minutes, the solution turned dark blue. After one hour, the solution was diluted with THF and stirred for an additional hour before cooling to -78 °C. It should be noted that solutions of samarium diiodide are very water and air sensitive and excess equivalents samarium diiodide are necessary in reactions, not only because in most cases two equivalents are required but also because of adventitious water may quench the reaction. The starting substrate and t-butanol were diluted with THF, added to the samarium diiodide solution, and generally, the reaction was slowly warmed to room temperature and allowed to stir overnight. The reactions were diluted with ether and then quenched with a small amount of water. Large amounts of celite were added to the solution and stirred for 2-4 hours or until the mixture was homogeneous. Then, the mixture was filtered through celite and the solvent evaporated to give an oily residue which was usually purified by column chromatography. In the majority of experiments, the products were not isolated, but were monitored by GC and crude NMR analysis and compared with isolated products from Chapter 3.

As a whole, the $SmI_2$ reactions appeared to be much cleaner, and resulted in mixtures which were easier to chromatograph than those of TBTH. Admittedly, the workup of the samarium reactions was difficult, and the products of the reactions with HMPA as a major part of the solvent were not isolated because of the difficulty in removing and handling the highly toxic and carcinogenic[61] HMPA solutions.

In the first study, α,β-unsaturated ester 158 was subjected to the reaction conditions described above, as shown in Scheme 4-3. Using samarium diiodide (4 equivalents) and t-butanol (2 equivalents) as a proton source in dilute THF (0.1 M), four products were formed in a 1.2 : 1.0 : 3.8 : 6.0 ratio in 82 % yield.

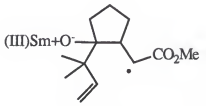



Scheme 4-3

The mono-cyclized and lactonized products, 171 and 172, were produced predominantly, while the bicyclic compounds, 159 and 160, which were the major products from the tin reaction, were minor products of the samarium reaction. Moreover, the formation of these products appears to be dependant on the concentration and the presence of t-butanol. Under slightly more dilute conditions (0.05 M), without t-butanol, the bicyclic products are not formed, and the mono-cyclized trans product 171 predominates as 61% of the reaction mixture. Additionally, with 2.5 equivalents of $SmI_2$, the same ratio of products is formed as with 4 equivalents. Unlike the tin method, only a small percentage of the products formed were the result of a tandem reaction.

The bicyclic compounds, 159 and 160, which were also formed in the TBTH reaction, were the result of a free radical tandem reaction. The other two products imply that the tandem reaction failed. One possible mechanistic explanation for this failure is that the intermediate radical (Figure 4-1) was rapidly reduced by another equivalent of $SmI_2$ before it had time to cyclize onto the sterically hindered nonactivated olefin.




**173**

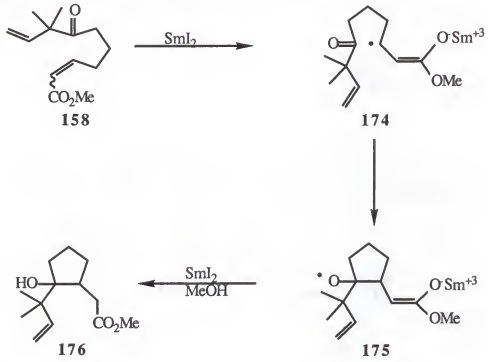
Figure 4-1

Ester stabilized radical

Samarium diiodide may have difficulty undergoing tandem-free radical reactions if the rate of reduction of the ester stabilized radical 173 is faster than the rate of the intramolecular cyclization of that radical (Scheme 4-3). Even the use only one equivalent of samarium diiodide did not circumvent this problem. When 1.2 equivalents of samarium diiodide was used in the reaction, starting material was not consumed, and only very minor amounts of products were observed. Curiously, the indane compound 161 created in the TBTH reaction was not observed in any reactions with $SmI_2$. While the same bicyclic products were produced in the TBTH and $SmI_2$ reactions they were only minor components in the samarium reaction and the major products indicate that $SmI_2$ under the above conditions is not effective at tandem cyclizations, and unfortunately it appears that although an excess of samarium diiodide is necessary for the reaction, it may reduce the radical to an anion and prevent the second cyclization.

It is not completely clear if the products in Scheme 4-3 resulted from the initial reduction of the ketone; another mechanistic possibility involves the initial reduction of the $\alpha,\beta$-unsaturated ester, as shown in Scheme 4-4. Because the ketone and the $\alpha,\beta$-unsaturated ester have similar reduction potentials[62] and the ketone is sterically hindered by the geminal methyls, the initial electron could have been transferred to the $\alpha,\beta$-unsaturated ester by $SmI_2$, forming samarium anion radical 174 which cyclizes onto the ketone producing 175. Additional reduction by $SmI_2$ to the alkoxide, and protonation by t-butanol would give the alcohol 176. It is clear that if the ester in 158 is reduced faster than the ketone, the cyclization onto the unactivated alkene will not take place. Thus, the Sm (III) enolate structure 175 does not close on the pendant olefin to produce a bicyclic product. In

support of this mechanism, Girard and coworkers,[63] reduced the double bond of α,β-unsaturated esters and acids with samarium diiodide

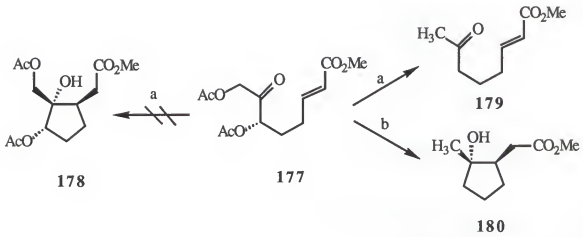



Scheme 4-4

Unfortunately this result has only been applied to aromatic olefins; aliphatic systems appear to require the addition of N, N-dimethylacetamide (DMA) or N, N-dimethylformamide (DMF) to facilitate reduction.[18(d)] However, it is a plausible explanation that the ester is reduced first.

This dilemma has been examined by Trivellas[57] and has yet to be completely resolved. As a mechanistic probe, a molecule which possesses both a ketone moiety and an α,β-unsaturated ester was derived from D-glucal (Scheme 4-5). The idea was to react the molecule with an excess of $SmI_2$ and on the basis of the structure of the isolated product(s) infer which carbonyl group was reduced preferentially. It has been demonstrated by Molander and Hahn[64] that α-acetoxy ketones rapidly eject the acetoxy functionalities when subjected to 2 equivalents of $SmI_2$-methanol. Thus,

the initial reduction of the ketone would not cyclize and would produce products 179 and 180, devoid of the acetate moieties. But, the one electron reduction of the unsaturated ester would cyclize and produce the complex cyclopentane 178. The study demonstrated that indeed the ketone was reduced first, and the products, 179 and 180, isolated from a 4 equivalent and 5 equivalent $SmI_2$ reduction respectively, are devoid of the acetoxy functions.



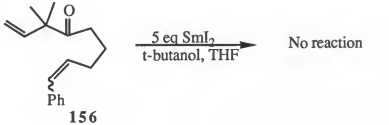

KEY: (a) $SmI_2$ (4 eq.), THF, MeOH; (b) $SmI_2$ (5 eq.), THF, MeOH.

Scheme 4-5

This seemed to indicate (once and for all) that the reduction must preferentially occur at the ketone functionality. But this experiment is not without flaws. Professor Albert Padwa suggested in a private communication that the ester may indeed accept the initial electron, but it transfers immediately through space to the ketone. The products from such a process would be identical to those occurring with the initial reduction of the ketone. Another more plausible difficulty with this system is the α-acetoxy functions may substantially reduce the reduction potential of the

ketone to the point that it becomes the electrophore. From these arguments it can be concluded that the electron may still be initially accepted by the α,β-unsaturated ester even if the study in Scheme 4-5 indicates otherwise.

The other substrate which was examined was the styrene stabilized system. When this compound (156) was subjected to the exact same conditions as the ester, no products were observed and only starting material was isolated from the reaction (Scheme 4-6).




**156**

Scheme 4-6

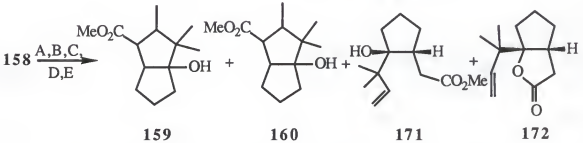
It was quite surprising that even in the presence of a five fold excess of samarium diiodide, the ketone remained intact. Because the ketone functionalities of the ester and the styrene system are exactly the same, it was expected that the carbonyl of 156 would have, at the very least, been reduced. With TBTH, this compound was also reluctant to reduce (see Scheme 3-18), and the equilibration observed in this system could have been the result of either reversible hydrostannation or reversible initial ring closure. This seems to confirm the earlier suspicion that in the case of the α,β-unsaturated ester, the ester olefin was initially reduced, and the major products were the result of a "reverse" mechanism, involving the initial reduction of the ester, followed by the cyclization onto the sterically hindered ketone.[65] It is a plausible concept that the initial coordination

occurs at the ester oxygen functionality, whether or not the initial reduction takes place there as well.

In the above examples, it seemed as if $SmI_2$ and TBTH were not acting in a similar fashion. It became necessary to investigate alternative reaction conditions in order to compare the two reagents on an equal basis. HMPA in small amounts is a frequent additive in $SmI_2$ reactions and it has been known to increase the rate of these reactions as well as improve the yields; however, no arguments about the exact nature of this effect have been set forth. Fevig et al. noted that HMPA was necessary for the formation of the product hypnophilin (Scheme 1-10).[27] Without HMPA, the reaction was sluggish, required reflux and gave the simple alcohol as the major product, and the expected tricyclic ketal as the minor product in extremely low yields. The behavior of samarium diiodide in HMPA-THF is completely different from its behavior in THF alone.

In this research, HMPA appears to be not only enhancing the stereoselectivity, but it also promoting the free radical reaction. When ester 158 was reacted with $SmI_2$ in 4.5 % HMPA-THF solution, without t-butanol, a large change in the ratio of the products was noted (Scheme 4-7, Method B). It appeared as if one product, the di-cyclized ester 159, was produced predominantly, while the amount of mono-cyclized products 171 and 172 was suppressed. In a 50 % HMPA-THF solution (Method C), the predominant product was once again the di-cyclized ester, 159, and the other components were produced only in minor amounts. Even with a large excess of $SmI_2$ the reaction in HMPA is mainly a one electron process, and the generated free radical appears to be abstracting a hydrogen atom from THF in the final step. The presence of t-butanol (Method D) did not appreciably change the ratio of the products, however the lactol 172 was

not observed in this reaction. An interesting observation is that the reaction in HMPA (50% HMPA-THF) produced one bicyclic product selectively. Without HMPA, the bicyclic products 159, and 160 were produced in the approximately equal ratio of 1.2:1. Regrettably, the stereochemistry of the major product (159) could not be elucidated by NOE studies, and remains a unassigned (even with the assistance of Professor Roy King, no NOE data could be obtained to support the assignment of stereochemistry). However, this effect has never been observed before with $SmI_2$ and we believe it is a significant finding.




159 160 171 172

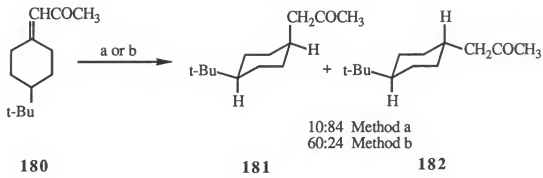
| Method | 159 | 160 | 171 | 172 |
|---|---|---|---|---|
| A | 1.2 | 1.0 | 3.8 | 6.0 |
| B | 21.3 | 2.5 | 12.8 | 1.0 |
| C | 18.9 | 1.8 | 1.4 | 1.0 |
| D | 11.3 | 1.0 | 1.5 | 0 |
| E | 1 | 1 | 0 | 0 |

KEY: (A) $SmI_2$ (4 eq), THF, t-BuOH; (B) $SmI_2$ (2 eq), THF, 4.5% HMPA-THF; (C) $SmI_2$ (5 eq), 50% HMPA-THF; (D) $SmI_2$ (5 eq), 50 % HMPA-THF, t-BuOH; (E) TBTH (2.5 eq), AIBN (0.2 eq), Benzene (0.05 M), reflux.

Scheme 4-7

Thus, the reaction of $SmI_2$ in HMPA appears to be a one electron process, and can be compared to the one electron reactions of TBTH. Collectively, these two reagents represent the reagents of choice in this tandem transformation and the HMPA/$SmI_2$ reagent combination appears to be superior to the TBTH reaction in Method E. It appears, then, that the HMPA is functioning in two capacities: it is increasing the stereoselectivity of the reaction and it is enhancing the "one-electron" nature of samarium diiodide.

HMPA is known to increase the stereoselectivity of other reactions. Most notably are the reactions of simple ester enolates. Yamaguchi and co-workers[65] noted the increase in diastereoselectivity in reactions in which HMPA had been added and ascribed the result to the interaction of the polar molecule at the transition state. Additionally, Helmchen et al.[66] noted an increase in selectivity with increasing concentrations of HMPA with lithium enolates. In another important study, House et al.[67] compared the reduction of enones with sodium or lithium in liquid ammonia to sodium or lithium in hexamethylphosphoramide. These reductions are very similar to the reductions of samarium diiodide. They found that the reductions with Na-HMPA yielded products containing a significant proportion of the less stable epimer than was found in the Na-$NH_3$ reactions. The reaction which showed the most pronounced stereoselectivity is the reaction of unsaturated ketone 180, as shown in Scheme 4-8. In this case, a significant amount of the less stable axial reduction product, 181, was formed at low temperatures. They noted that temperature and the presence of a proton donor, as well as other factors, governed the ratio of the products. The type of metal, however does not seem to affect the outcome of the reaction.




KEY: Method a) Na, t-BuOH in $NH_3$ (l)-THF at -33° C; Method b) Na, t-BuOH in HMPA at -33° C

Scheme 4-8

It is not at all improbable that the radical anion of HMPA is in fact the reacting species in the above research and in the reactions with samarium diiodide as well. The high dielectric constant of HMPA favors electron transfer reactions, and the solutions of HMPA with sodium metal are deep blue, which may reflect the solvation and rapid transfer of electrons. It is well-established that alkali metals react with a variety of organic molecules, such as polynuclear aromatics and ketones to yield radical ions and ketyls.[68] In fact, solvents such as THF and benzene are purified by the distillation from a benzophenone ketyl, produced by the reaction of sodium metal and benzophenone. The ketyl radical has also been observed in trialkyl and triaryl[69] phosphine oxides, so HMPA could also form a ketyl under the proper conditions. Although the reduction potential for $Sm^{+3}$ (-1.55 eV)[18(b)] is less than the reduction potentials for lithium and sodium metal, (-3.04 eV, and -2.71 eV),[70] it is plausible that the HMPA initially accepts an electron from $SmI_2$, forms an "intermediate" ketyl (Figure 4-2) and then it is this ketyl which reacts with substrate to yield the observed products. This could explain why different products are observed when HMPA is added to the solutions of $SmI_2$. Thus. the

behavior of samarium may be governed by its interaction with HMPA, and the products may be the indirect result of an initial samarium electron transfer reaction to HMPA.

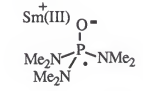



Figure 4-2

HMPA ketyl

In summary, samarium diiodide in HMPA undergoes reactions similar to tributyltin hydride, and its behavior also mirrors that of the alkali metals such as sodium or lithium. In most reactions, samarium diiodide appears to first coordinate with oxygen and then transfer an electron to the substrate to give a samarium ketyl. Unlike the behavior of TBTH, $SmI_2$/THF produces mainly mono-cyclized products and the products resulting from a tandem, one-electron cyclization are observed, but do not predominate. The carbonyl of the styrene stabilized example failed to even be reduced by both the TBTH and $SmI_2$/THF and this leads us to conclude that in the ester case the electron from $SmI_2$ may first be injected into the $\alpha,\beta$ unsaturated ester system, or at the very least, the initial coordination occurs at the ester site. Thus, the mechanism of $SmI_2$ in THF may be opposite of its mechanism in HMPA. Additionally, the stereoselectivity of the reactions were enhanced by the addition of HMPA to the solution. It appears that $SmI_2$ is functioning in a similar fashion to metals commonly used in dissolving metal reductions, and that the HMPA may be functioning as an electron transfer agent through its ketyl species. In any case, this last result may lead to additional uses for this already practical reagent.

# CHAPTER 5
# SUMMARY

The studies described here in are an attempt to expand the realm of free radical chemistry in synthesis. The effectiveness of these reactions is reflected in the shear number of complex syntheses which contain a free radical reaction in the synthetic sequence. Many synthetic chemists have demonstrated the simple elegance of the free radical reaction in the synthesis of complex polycyclic molecules. The mild reactions conditions, and the ability to control reactivity, stereoselectivity, and regioselectivity in these reactions are certainly different qualities from its original "unruly" reputation of free radicals 40 years ago.

This work utilized two reagents, tributyltin hydride and samarium diiodide, to study the coupling of unsaturated carbon centers in the formation of five-membered rings. These reagents, which function by completely different mechanisms are similar in that they both engage in the reactions of dehalogenation and reduction of carbonyls.

In the first study, tributyltin hydride (TBTH) was used to couple terminal alkynes with oxime ethers to afford highly functionalized cyclopentanoids with a protected amino group alpha to the exo-methylene unit. This hydrostannation-type reaction revealed that the vinyl radical can also be utilized in coupling reactions. The reactions were generally high yielding, and it appears that substrates which posses a oxime unit beta to a aromatic ring may not be suited for this reaction because of the possibility

of competing β–scission process. This coupling reaction, however appears to be a viable and practical method in obtaining amino cyclopentanoids.

The use of the tin ketyl in synthesis is limited to a few isolated examples. The application of this radical anion in tandem reactions has never even been studied and was the focus of the second part of this work. The tandem cyclization was accomplished by the action of the tributyltin radical on a ketone or aldehyde carbonyl which was tethered to activated and non-activated alkenes. Activated (electrophilic) alkenes such as styrenes and α,β-unsaturated esters were used to increase the likelihood of the first cyclization. The arrangement of the alkene units within the molecule was varied in order to to generate the ring systems of "separated," "spiro" and "fused" if the reaction was successful. The "fused" and "spiro" precursors afforded the tandem ring products in moderate yields; however the "separated" ring example appeared to be too sterically hindered to undergo the second cyclization and yielded only monocyclized products. Interestingly, the phenyl group does not appear to activate the olefin nearly as much as the ester functionality because some of the substrates which contained this unit were inherently resistant to cyclization. However, the examples that did cyclize gave well functionalized products and it appears that the tin ketyl is well suited for tandem cyclizations.

The third chapter compared the reactivity of tin and samarium ketyls. This study revealed that $SmI_2$ in THF alone is not as effective as the TBTH reaction. The second equivalent of $SmI_2$ may readily reduce the intermediate radical to give an anion and consequentially, may kill the tandem reaction. It is not entirely clear, however, if the $SmI_2$ is first reducing the ketone or the ester functionality. In HMPA, $SmI_2$ is superior

to TBTH and it behaves in a similar manner to metals such as lithium or sodium, and the observed stereoselective formation of the bicyclic product 159 may be the result of an intermediate HMPA ketyl and not from the direct interaction of samarium with the substrate. In any case, these findings expand the utility of this reagent combination.

In conclusion, these three sets of studies demonstrate the effectiveness of various combinations acceptors and precursors in free radical cyclization reactions. By simply varying the types of unsaturated units, their relative positioning, and the reaction conditions in these reactions different products were obtained. It was demonstrated that a wide variety of structures, ranging from simple cyclic esters to phenyl substituted spiro compounds are accessible through the free radical chemistry of TBTH and $SmI_2$. These are the first examples of such transformations and will provide additional weaponry in the synthetic arsenal.

# CHAPTER 6
# EXPERIMENTAL SECTION

## General

Melting points were determined on a Thomas-Hoover capillary melting point apparatus and are uncorrected. Infrared spectra were recorded on a Perkin-Elmer 283B spectrophotometer and are reported in wave numbers ($cm^{-1}$). Nuclear magnetic resonance (NMR) spectra were recorded at 300 MHz on a Varian VXR-300 (300 MHz) spectrometer and a General Electric QE 300 spectrometer. $^{13}C$ NMR spectra were recorded at 75 MHz on a Varian VXR-300 spectrometer and on a General Electric QE 300 spectrometer. Chemical shifts are reported in ppm down field ($\delta$) relative to tetramethylsilane ($(CH_3)_4Si$) as an internal standard in $CDCl_3$. Mass spectrums and exact mass measurements were performed on Finnigan MAT95Q, Finnigan 4515, or Finnigan ITD mass spectrometers. Elemental analysis was performed by Atlantic Microlab, Inc., Norcross, GA 30091.

All reactions were run under an inert atmosphere of argon using flame-dried apparatus. All reactions were monitored by thin layer chromatography (TLC) and judged complete when starting material was no longer visible in the reaction mixture as spotted on TLC. All yields reported refer to isolated material judged to be homogeneous by thin layer chromatography and NMR spectroscopy. Temperatures above and below ambient temperature refer to bath temperatures unless otherwise stated.

Solvents and anhydrous reagents were dried according to established procedures by distillation under nitrogen from an appropriate drying agent: ether, benzene, and THF from benzophenone ketyl; dichloromethane from $CaH_2$. Other solvents were used "as received" from the manufacturer.

Analytical TLC was performed using E. Merck precoated silica gel plates (0.25 mm) using phosphomolybdic acid in ethanol as an indicator. Column chromatography was performed using E. Merck silica gel 60 (230-400 mesh) by standard flash and suction chromatographic techniques.[71]

All GC experiments were performed on a Varian 3500 capillary gas chromatograph using a J & W fused silica capillary column (DB5-30W; film thickness 0.25 micron).

## Experimental Procedures and Results

### Ethyl 2-carboethoxy-4,4-diethoxybutanoate (73)

To a stirred slurry of sodium hydride (162 mg; 4.06 mmol) in toluene (0.65 M, 6.24 mL), was added diethyl malonate (72) (500 mg; 3.12 mmol). After 20 minutes, bromoacetaldehyde diethyl acetal (0.934 mL, 6.24 mmol) and 15-crown-5 (0.682 mL, 3.43 mmol) were added. The resulting mixture was refluxed for 48 hours and then diluted with ethyl acetate (50 mL) and brine solution (15 mL). This mixture was extracted with ethyl acetate (3 x 50 mL). The ethyl acetate layers were combined and dried over anhydrous sodium sulfate. The solvent was removed under reduced pressure and the residue purified by column chromatography giving 730 mg of clear oil (84.7%): Rf 0.35 (20% diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) $\delta$ 4.54 (t, 1 H, J = 5.6 Hz), 4.20 (m, 4 H), 3.65 (m, 2 H), 3.51 (m, 3 H), 2.23 (d of d, 2 H, J = 5.7 Hz, 1.5 Hz),

1.27 (t, 6 H, J = 7.2 Hz), 1.20 (t, 6 H, J = 6.9 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 169.26, 100.77, 61.85, 61.34, 48.12, 32.77, 15.17, 14.01; IR (neat oil) 2979, 2934, 2903, 1732, 1445, 1371, 1337, 1270, 1238, 1128, 1062 $cm^{-1}$; mass Spectrum (EI): m/z (relative intensity) 275 (m+,0.25), 231 (89), 157 (69), 103 (100), 75 (41), 47 (52); analysis, calculated for $C_{13}H_{24}O_6$: C: 56.49%, H: 8.76%; found C: 56.38%, H: 8.78%.

Ethyl-2-carboethoxy-2(2,2-diethoxyethyl)-pent-4-yne-oate (74)

Ethyl 2-carboethoxy-4,4-diethoxybutanoate (73) (359 mg, 1.30 mmol) was added to a stirred slurry of sodium hydride (63 mg, 1.58 mmol) in THF (0.25 M; 5.2 mL) under argon. After approximately 30 minutes, propargyl bromide (0.232 mL, 2.60 mmol) was added to the flask. The reaction was stirred for 18 hours at room temperature and quenched with brine (10 mL). The mixture was extracted with ethyl acetate (3 x 75 mL). The ethyl acetate layers were combined, dried over anhydrous sodium sulfate and the solvent was removed in vacuo to give an oil which was purified by column chromatography to give 350 mg (85.7%): Rf 0.42 (20% diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 4.56 (t, 1 H, J = 5.7 Hz), 4.20 (m, 4 H), 3.65 (m, 2 H), 3.46 (m, 2 H), 2.43 (d, 2 H, J = 2.7 Hz), 2.29 (d, 2 H, J = 5.7 Hz), 2.02 (t, 1 H, J = 3.0 Hz), 1.25 (t, 6H, J = 7.2 Hz), 1.18 (t, 6 H, J = 6.9 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 169.75, 100.10, 78.91, 71.45, 62.02, 61.43, 54.43, 35.59, 22.94, 15.02, 13.86; IR (neat oil) 3276, 2978, 2934, 2903, 1736, 1465, 1445, 1371, 1345, 1320, 1286, 1249, 1190, 1130, 1019, 998, 645 $cm^{-1}$; mass spectrum (CI) m/z (relative intensity), 316 (M+1, 0.22), 269 (100); (EI)

269 (100), 103 (91), 75 (24), 47 (36); analysis, calculated for $C_{16}H_{26}O_6$: C: 61.11, H: 8.34; found C: 61.36, H: 8.40.

Ethyl-2-carboethoxy-2-(2-ethanal) pent-4-yne-oate (75)

Ester (74) (231 mg, 0.735 mmol) was dissolved in 15 mL of acetone and para-toluene sulfonic acid monohydrate (28.0 mg, 0.146 mmol) was then added. The reaction was stirred at room temperature for 18 hours, and then quenched with aqueous saturated sodium bicarbonate (5 mL) solution and extracted with ethyl acetate. The combined layers were dried over anhydrous sodium sulfate and concentrated "in vacuo." After flash chromatography 168 mg (95.0%) of clear oil was obtained: Rf 0.21 (20% diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) $\delta$ 9.77 (d, 1 H, J = 0.9 Hz), 4.24 (q, 4 H, J = 7.2 Hz), 3.25 (d, 2 H, J = 0.6 Hz), 2.98 (d, 2 H, J = 2.6 Hz), 2.05 (t, 1 H, J = 2.6 Hz), 1.26 (t, 6 H, J = 7.6 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$ ) $\delta$ 198.49, 168.75, 78.63, 72.07, 62.21, 53.97, 45.86, 23.77, 13.86; IR (neat oil) 3283, 2984, 1740, 1368, 1287, 1198, 1019 $cm^{-1}$; mass spectrum (EI), m/z (relative intensity) 241 (m+1, self CI, 30), 173 (100),167 (49), 139 (28), 127 (78), 121 (42), 110 (33), 99 (26), 93 (36), 82 (29), 65 (65); exact mass calculated for $C_{16}H_{16}O_5$: 240.0997; found: 240.0977; analysis, calculated for $C_{12}H_{16}O_5$: C: 59.98, H: 6.72; found C: 59.79, H: 6.76.

Benzyl oxime (76)

Aldehyde 75 was dissolved in chloroform (2.2 mL) and O-benzylhydroxyamine hydrochloride (97.9 mg, 0.613 mmol), and pyridine (0.0902 mL, 1.11 mmol) were added and stirred for 18 hours. Aqueous

saturated sodium bicarbonate (5 mL) was added and the mixture was extracted with ethyl acetate and the combined organic layers were dried over anhydrous $Na_2SO_4$. The solvent was removed "in vacuo" and the resulting oil was then purified by flash chromatography to yield 166 mg of a 50:50 mixture of cis and trans isomers (86.5 %). Physical data are reported for the cis isomer: Rf 0.55 (20% diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 7.45 (t, 1 H, J = 6.0 Hz), 7.33 (m, 5 H), 5.03 (s, 2 H), 4.16 (m, 4 H), 2.92 (d, 2 H, J = 6.0 Hz), 2.84 (d, 2 H, J = 2.7 Hz), 2.03 (t, 1 H, J = 2.7Hz), 1.22 (t, 6 H, J = 7.2 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 169.04, 146.55, 137.61, 128.30, 128.21, 127.76, 78.49, 75.79, 71.83, 61.88, 55.83, 32.57, 23.46, 13.93; IR (neat oil) 3288, 2982, 1732, 1454, 1368, 1286, 1210, 1096, 1052, 1016, 699; mass spectrum (CI) m/z (relative intensity) 346 (m+1, 100); exact mass, calculated for $C_{19}H_{23}NO_5$: 345.1576; found: 345.15846.

Cyclic product of Benzyl oxime (77)

Benzyl oxime 76 (97.0 mg, 0.280 mmol) was placed in a 50 mL flame dried flask and was diluted with benzene (0.02M; 14 mL). Then tributyltin hydride (147 mg, 0.506 mmol) and 2, 2'-azobis[2-methylpropionitrile] (9.0 mg, 0.056 mmol) were added and the mixture was degassed with argon for 30 minutes. The degassing tube was removed and the reaction was refluxed for 24 hours at 80 °C. The reaction was monitored by thin layer chromatography. After the disappearance of the starting material the benzene was removed "in vacuo" and the residue was then dissolved in methanol (0.56 mL; 0.50 M). To this solution, a catalytic amount of acetic acid was added and the solution stirred for 24 hours.

When the reaction was complete the solvent was removed "in vacuo" and the residue purified by flash chromatography to give 51 mg of title compound (57%) and 7 mg of recovered starting material: Rf 0.24 (20% diethyl ether-hexane); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.35 (m, 5 H), 5.48 (s, 1 H), 5.12 (d, 2 H, J = 9.3 Hz), 4.70 (s, 2 H), 4.27 (m, 4 H), 3.98 (s, 1 H), 3.13 (m, 1 H), 2.83 (m, 1 H), 2.58 (d of d, 1 H, J = 13.7 Hz, 7.1 Hz), 2.36 (d of d, 1H, J = 5.29 Hz, 13.8 Hz), 1.35 (t, 6 H, J = 8.6 Hz); 75 MHz $^{13}$C NMR ($CDCl_3$), δ 171.61, 147.47, 137.79, 128.41, 128.30, 127.74, 110.3, 76.51, 63.25, 61.54, 58.26, 39.75, 38.32, 13.97; IR (neat oil) 2982, 2935, 1731, 1452, 1367, 1233, 1190, 1095, 1068, 1025, 906, 749, 699 $cm^{-1}$; mass spectrum (EI) m/z (relative intensity), no $M^+$ observed, 91 (100), 79 (36), 77 (27); exact mass calculated for $C_{19}H_{25}NO_5$: 347.1732; found: 347.1735.

Benzyl oxime of Cyclopentanecarboxylic acid 2-oxo-1-(3-butyl) methyl ester (80)

2-Carbomethoxy-2-(3-butynyl)cyclopentanone (79) (105 mg, 0.540 mmol) was dissolved in $CHCl_3$ (0.45 M; 1.2 mL). Pyridine (0.105 mL, 1.28 mmol) and O-benzylhydroxylamine hydrochloride (164 mg, 1.03 mmol) were added and the reaction mixture was stirred for 17 hours at 50 °C. After this time, TLC indicated that the reaction was complete and the reaction was quenched with saturated solution of $NaHCO_3$ (1 mL) and extracted with diethyl ether. The combined ether washings were dried over anhydrous sodium sulfate and and then concentrated. After flash chromatography 147 mg (86.0%) of pure product was obtained: Rf 0.46 (30 % diethyl ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.32 (m, 5 H); 5.10 (s, 2 H), 3.65 (s, 3 H), 2.63 to 1.62 (m, 11 H); 75 Hz $^{13}$C NMR ($CDCl_3$), δ 173.54, 165.06, 138.07, 128.18, 128.07, 127.62, 84.06,

75.98, 68.31, 55.89, 52.28, 35.64, 34.35, 28.01, 21.81, 14.57; IR (neat oil) 2954, 1732, 1453, 1237, 1200, 1155, 1017 $cm^{-1}$; mass spectrum (EI) m/z (relative intensity), 298 (m+, 1.3), 134 (38), 92 (26), 91 (100), 77 (28), 65 (26); exact mass for $C_{18}H_{20}NO_3$ (loss of hydrogen): 298.1440; found: 298.1437.

2-Carbomethoxy-2-(3-butynyl)cyclohexanone (82)

Compound 81, 2-carbomethoxycyclohexanone, (628 mg, 4.02 mmol) was added to a slurry of sodium hydride (230 mg, 5.76 mmol) in toluene (0.50M, 8.5 mL). 15-Crown-5 (507 mg, 2.30 mmol) was added and the reaction mixture was stirred for 15 minutes. Then 4-iodobutyne (1.22 g, 6.77 mmol) was added. After 24 hours at reflux, an additional amount of 4-iodobutyne (270 mg, 1.50 mmol) was added and refluxed for an additional 24 hours. After TLC indicated the completion of the reaction, the mixture was quenched with water and extracted with ethyl acetate. Evaporation of the solvent and isolation by flash chromatography yielded 350 mg (42%) of product: Rf 0.33 (20% diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) $\delta$ 3.75 (s, 3 H), 2.49 to 1.95 (m, 13 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 207.19, 171.85, 83.64, 68.41, 60.05, 52.29, 40.86, 36.11, 33.67, 27.40, 22.36, 13.99; IR (neat) 3288, 2949, 1712, 1436, 1238, 1219, 1199, 1139, 642; mass spectrum (EI) m/z (relative intensity), 208 (m+, 0.22), 143 (100), 103 (54), 71 (36), 59 (27); exact mass calculated for $C_{12}H_{16}O_3$: 208.1099; found: 208.1085.

Benzyl oxime of 2-carbomethoxy-2-(3-butynyl)cyclohexanone (83)

Alkyne 82 (74.0 mg, 0.355 mmol) was dissolved in chloroform (0.46M; 0.78 mL). Pyridine (70.2 mg, 0.877 mmol) and O-benzylhydroxylamine hydrochloride (113 mg, 0.710 mmol) was then added and the reaction was heated for 6 hours at 50 °C and then stirred at room temperature for 17 hours. The reaction mixture was quenched with aqueous saturated sodium bicarbonate solution (1 mL) and extracted with diethyl ether. The combined diethyl ether layers were dried over anhydrous sodium sulfate and then removed "in vacuo." Subsequent purification by flash chromatography yielded 85 mg of higher Rf isomer and 18 mg of lower Rf isomer (91%). Physical data for the major isomer are as follows: Rf 0.48 (30 % diethyl ether-hexanes); 300 MHz $^{1}H$ NMR ($CDCl_3$) $\delta$ 7.35 (m, 5 H), 5.09 (s, 2 H), 3.68 (s, 3 H), 3.2 (m, 1 H), 2.35-1.30 (m, 12 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 173.76, 158.75, 137.35, 128.15, 127.54, 84.47, 75.68, 68.03, 53.26, 52.01, 35.97, 34.72, 25.49, 23.82, 22.69, 14.29; IR (neat) 3250, 2950, 2800, 1765, 1400, 1300; mass spectrum (EI) m/e (relative intensity), 313 (m+, 0.11), 91 (100); exact mass calculated for m-1 (loss of hydrogen) $C_{19}H_{22}NO_3$: 312.1599; found: 312.1595.

Bicyclic product of benzyl oxime (84)

Benzyl oxime of 2-carbomethoxy-2-(3-butynyl) cyclopentanone (80) (87.0 mg, 0.290 mmol) and benzene (0.02 M; 15 mL) were placed in a flame dried 50 mL round bottom flask. Tributyltin hydride (0.093 mL, 0.305 mmol) and 2, 2'-azobis[2-methylpropionitrile] (11 mg, 0.067 mmol) were then added and the mixture was degassed with bubbling argon for 30

minutes. After removing the degassing tube, the reaction was heated at 80 °C for 10 hours. The benzene was then removed "in vacuo" and the residue was diluted with $CH_2Cl_2$ (0.05 M; 6 mL) and 4 drops of acetic acid was added and the mixture was stirred for 6 hours at room temperature. The solvent was removed "in vacuo" and the residue was subjected to flash chromatography. The clear oil weighed 78 mg (90 %): Rf 0.48 (30% diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 7.40 (m, 5 H), 6.25 (s, 1 H), 5.20 (s, 1 H), 5.08 (s, 1 H), 4.65 (s, 2 H), 3.61 (s, 3 H), 2.69 to 1.20 (m, 10 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 176.96, 155.60, 138.00, 128.10, 127.63, 127.31, 107.56, 81.37, 76.41, 60.17, 51.75, 38.82, 38.22, 34.28, 32.50, 23.37; IR (neat) 2949, 1733, 1713, 1454, 1433, 1270, 1148, 698; mass spectrum (EI) m/z (relative intensity), 301 (m+, 20), 119 (26), 91 (100); exact mass calculated for $C_{18}H_{23}NO_3$: 301.1677; found: 301.1674.

Bicyclic product of benzyl oxime (85)

Oxime 83 (90.0 mg, 0.287 mmol) was placed in a flame dried flask and dissolved in benzene (0.02M; 14.0 mL). Tributyltin hydride (0.085 mL, 0.302 mmol) and 2, 2'-azobis[2-methylpropionitrile] (11 mg, 0.067 mmol) were then added and the mixture was degassed with bubbling argon for 30 minutes. After removing the degassing tube, the reaction was heated at 80 °C for 10 hours. After this time it was checked by TLC and the starting material had been consumed. The benzene was removed "in vacuo" and the residue was diluted with $CH_2Cl_2$ (6 mL; 0.05 M) and 4 drops of acetic acid were added and the mixture was stirred for 6 hours. The solvent was then removed "in vacuo" and the residue was subjected to flash

chromatography. The clear oil weighed 74 mg (82 %): Rf 0.41 (30 % diethyl ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.28 (m, 5 H), 6.04 (s, 1 H), 5.17 (d, 2 H, J = 10.7 Hz), 4.54 (d, 2 H, J = 4.4 Hz), 3.64 (s, 3 H), 2.70 to 2.20 (bm, 4 H), 1.95 to 1.20 (bm, 8 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 175.79, 157.79, 149.45, 138.05, 128.39, 128.10, 127.45, 110.39, 77.00, 79.97, 54.87, 51.46, 33.46, 31.49, 27.94, 27.78, 22.39, 22.28; IR (neat) 2936, 1725, 1452, 1289, 1241, 1148, 1021, 893; mass spectrum (EI) m/z (relative intensity) 315 (m+, 7.9), 135 (25), 133 (60), 91 (100); exact mass calculated for $C_{19}H_{25}NO_3$: 315.1834; found: 315.1834.

9-Acetyl-9-(3-butynyl)fluorene (87)

To a solution of $K_2CO_3$ (240 mg, 2.28 mmol) in methanol (3.2 mL) was added 9-acetyl fluorene (86) (237 mg, 1.14 mmol) in acetone (3.2 mL). 4-Iodobutyne (410 mg, 2.28 mmol) was added and the reaction was refluxed for 20 hours. The reaction mixture was quenched with water (1 mL) after TLC indicated the completion of the reaction. It was then extracted with ethyl acetate and the combined ethyl acetate layers were dried over anhydrous sodium sulfate. The solvent was removed "in vacuo" and the residue purified by flash chromatography to yield 220 mg (74%) of a yellow solid (mp. 107-109 °C): Rf 0.33 (30% diethyl ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.82 (d, 2 H), 7.47 (m, 2 H), 7.35 (d, 2 H), 2.65 (m, 2 H), 1.80 (t, 1 H), 1.45 (s, 3 H), 1.42 (m, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 206.42, 144.15, 142.01, 128.56, 128.06, 123.82, 120.51, 83.88, 68.09, 67.79, 32.46, 25.18, 13.08; IR (KBr pellet) 3272, 1699; mass spectrum (EI) m/z (relative intensity), 260 (m+, 22), 217

(100), 202 (65), 178(99), 43 (38); analysis calculated for $C_{19}H_{16}O$: C: 87.66, H: 6.19; found: C: 87.87, H: 6.33.

Benzyl oxime of 9-acetyl-9-(3-butynyl)fluorene (88)

9-acetyl-9-(3-butynyl)fluorene (87) (160 mg, 0.615 mmol) was dissolved in $CHCl_3$ (0.30 M; 2.0 mL). O-benzylhydroxylamine hydrochloride (245 mg, 1.54 mmol) and pyridine (146 mg, 1.84 mmol) was added and the reaction was heated at reflux for 1.5 hours. The reaction mixture was then quenched with aqueous saturated solution of $NaHCO_3$ (1 mL) and extracted with ethyl ether. The combined organic layers were dried over anhydrous sodium sulfate. The solvent was removed "in vacuo" and the oil was purified by flash chromatography to give 240 mg of product (90%): Rf 0.50 (20 % diethyl ether-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) $\delta$ 7.70 (d, 2 H, J = 9.5 Hz), 7.30 (m, 11 H), 5.24 (s, 2 H), 2.57 (m, 2 H), 1.76 (t, 1 H, J = 2.5 Hz), 1.39 (m, 2 H), 1.12 (s, 3 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 158.26, 146.48, 141.53, 138.44, 128.27, 128.12, 128.07, 127.82, 127.59, 123.95, 120.07, 84.60, 75.79, 67.67, 60.12, 33.77, 13.31, 12.11; IR (neat) 3283, 1448, 738, 618; mass spectrum (CI) m/z (relative intensity), 366 (m+1, 100), 217 (56); analysis calculated for $C_{26}H_{23}NO$: C: 85.44, H: 6.35, N: 3.83; found: C: 85.25, H: 6.39, N: 3.82.

Rearranged oxime (90)

Alkyne 88 (137 mg, 0.375 mmol) was placed into a flame-dried round bottom flask. Benzene (19.0 mL; 0.02 M), 2,2'-azobis[2-methylpropionitrile] (12 mg, 0.075 mmol), and tributyltin hydride (124

mg, 0.412 mmol) were then added and the mixture was degassed with bubbling argon for 30 minutes. The degassing tube was removed and the reaction was refluxed for 24 hours. The solvent was removed "in vacuo" and the resulting oil was diluted with $CH_2Cl_2$ (0.03 M; 12 mL) and a catalytic amount of acetic acid was added and the reaction was stirred for 20 hours. The solvent was removed "in vacuo" and the residue was purified by column column chromatography to give an 82 mg of an oil (58 %): Rf 0.25 (30 % benzene hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) $\delta$ 7.31 (m, 12 H), 7.04 (m, 1 H), 5.17 (s, 2 H), 4.86 (s, 1 H),4.65, (s, 1 H), 3.38 (d of d, 1 H), 2.45 (m, 2 H), 2.24 (m, 1 H), 1.70 (m, 1 H), 1.50 (s, 3 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 159.39, 149.35, 144.10, 142.16, 139.94, 138.62, 138.60, 129.33, 128.97, 128.23, 128.05, 127.98, 127.62, 127.53, 127.43, 127.13, 126.20, 126.10, 115.24, 75.49, 47.21, 35.72, 31.98, 15.96; IR (neat) 3048, 2919, 1439, 1368; mass spectrum (EI) m/z (relative intensity), 367 (m+, 7), 91 (100); exact mass calculated for $C_{26}H_{25}NO$: 367.1936; found: 367.1942.

2-(N-propynyl)-aminoacetophenone (95)

A mixture of 2-aminoacetophenone (789 mg, 5.84 mmol) and propargyl bromide (340 mg, 2.33 mmol) was placed into a flask and heated to 90 °C for 2 hours. To the reaction was added NaOH (20% v/v aq; 1 mL) and $ZnCl_2$ (aq. sat.; 1 mL). The solid was washed five times with boiling hexanes and the combined washings were then washed with deionized water (15 mL) and $NH_4OH$ (5 % v/v aq; 30 mL). The organic layers were dried over anhydrous $K_2CO_3$. Evaporation of the solvent yielded a residue which was purified by flash chromatography to give 229 mg (57 %) of

yellow solid (mp. 72.5-73.5 °C): Rf 0.50 (30 % diethyl ether-hexanes, catalytic amount of $NH_4OH$); 300 MHz $^1H$ NMR ($CDCl_3$) δ 9.0 (1 H, bs), 7.75 (d, 1 H, J = 8.0 Hz), 7.41 (t, 1 H), 6.75 (d, 1 H, J = 8.5 Hz), 6.67 (t, 1 H), 4.01 (q, 2 H, J = 2.4 Hz, 5.6 Hz), 2.56 (s, 3 H), 2.21 (t, 1 H, J = 2.2 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 200.91, 149.68, 134.87, 132.57, 118.37, 115.14, 111.86, 80.16, 71.12, 32.04, 27.85; IR (KBr pellet) 3315, 3275, 1626, 1560, 1515, 1223; mass spectrum (EI) m/z (relative intensity), 173 (m+, 34), 172 (39), 158 (37), 130 (100), 103 (23), 77 (41), 43 (56); analysis, calculated for $C_{11}H_{11}NO$: C: 76.28, H: 6.40 , N: 8.09; found C: 75.68, H: 6.37, N: 7.86.

Oxime of 2-(N-propynyl)-aminoacetophenone (96)

2-(N-propynyl)-aminoacetophenone (103 mg, 0.577 mmol) was dissolved in $CHCl_3$ (0.30 mL, 1.92 M). O-benzylhydroxylamine hydrochloride (184 mg, 1.15 mmol) and pyridine (114 mg, 1.44 mmol) was added and the mixture was heated for 24 hours at 50 °C. The reaction was quenched with aqueous saturated $NaHCO_3$ (1 mL) and extracted with diethyl ether. The ether was concentrated and removed under reduced pressure and the crude sample was purified by flash chromatography yielding 150 mg (94%) of a yellow solid (mp. 73.5-75.5 °C): Rf 0.47 (30 % diethyl ether-hexanes, trace of $NH_4OH$); 300 MHz $^1H$ NMR ($CDCl_3$) δ 7.57 (bs, 1 H), 7.38 (m, 7 H), 6.62 (m, 2 H), 5.20 (s, 2 H), 3.82 (m, 2 H), 2.32 (s, 3 H), 2.18 (t, 1 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 157.50, 145.79, 138.14, 129.82, 128.95, 128.46, 128.34, 127.90, 118.60,116.17, 111.26, 81.03, 76.02, 70.71, 32.69, 13.42; IR (KBr pellet) 3290, 1605, 1568, 1518, 1015, 933, 909, 891, 745, 699, 646, 604;

mass spectrum (EI) m/z (relative intensity), 281 (m+, 0.16), 278 (26), 171 (100), 156 (24), 91 (89), exact mass calculated for $C_{18}H_{18}N_2O$: 278.1419; found: 278.1426.

Oxime of 2' (N-propenyl)-aminoacetophenone (98)

The oxime of 2'-(N-propynyl)-aminoacetophenone (96) (90 mg, 0.323 mmol) was placed in a flame-dried flask. Benzene (16 mL; 0.02 M), tributyltin hydride (0.157 mL, 0.582 mmol), and 2,2'-azobis[2-methylpropionitrile] (10 mg, 0.065 mmol) were added. The resulting solution was degassed for 30 minutes with bubbling argon. Then, the degassing tube was removed and the mixture was heated for 12 hours at 80 °C. The benzene was evaporated and the residue was stirred in $CH_2Cl_2$ (11 mL; 0.03 M) with a catalytic amount of acetic acid. After it was determined by TLC that the reaction was complete, the solvent was removed "in vacuo" and the residue was subjected to flash chromatography to give 54 mg of a yellow oil (60%): Rf 0.50 (30 % diethyl ether-hexanes, catalytic amount of $NH_4OH$); 300 MHz $^1H$ NMR ($CDCl_3$) $\delta$ 7.51 (bs, 1H), 7.35 (m, 7 H), 6.61 (m, 2 H), 5.78 (m, 1 H), 5.17 (s, 2 H), 5.23 to 5.07 (m, 2 H), 3.70 (m, 2 H), 2.35 (s, 3 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 157.86, 146.81, 138.19, 135.19, 129.82, 128.96, 128.41, 128.10, 127.79, 117.73, 115.71, 115.10, 111.10, 75.90, 45,75, 13.40; IR (neat) 3302, 2924, 2854, 1605, 1568, 1520, 1497, 1452, 1366, 1333, 1315, 1279, 1237, 1051, 1014, 930, 888, 742, 698, 607; mass spectrum (EI) m/z (relative intensity), 280 (m+, 25), 173 (97), 156 (46), 91 (100), 77 (29), exact mass calculated for $C_{18}H_{20}N_2O$: 280.1575; found: 280.1582.

1-Phenyl-5-hexen-1-ol (124)

Pentenyl magnesium bromide (47.2 mL, 23.61 mmol) was added dropwise to a solution of benzaldehyde (2.00 mL, 19.67 mmol) in THF (19.7 mL, 1.0 M) at 0 °C. After stirring at room temperature overnight, the reaction was quenched by the addition of aqueous saturated ammonium chloride solution (5 mL). The aqueous layer was extracted with ether and the combined ether extracts were dried over anhydrous sodium sulfate. Removal of the solvent gave an oil, which was subjected to suction chromatography to yield 3.17 g of a clear oil (92 %): Rf 0.31 (20% ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 5.71 (m, 1 H), 4.88 (m, 2 H), 4.57 (m, 1 H), 2.00 (m, 3 H), 1.68 (m, 2 H), 1.37 (m, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 144.81, 138.56, 128.43, 127.50, 125.87, 114.67, 74.49, 38.46, 33.56, 25.06; IR (neat) 3356, 2935, 2860, 1640, 1493, 1453, 1063, 1027, 994, 911; mass spectrum (EI) m/z (relative intensity), 176 (m+, 12), 133 (44), 120 (24), 107 (100), 79 (56); analysis calculated for $C_{12}H_{16}O$: C: 81.77, H: 9.15; found: C: 81.82, H: 9.21.

1-Phenyl-5-hexen-1-one (125)

Alcohol 124 (1.68 g, 9.54 mmol) was dissolved in methylene chloride (19.0 mL; 0.50 M). Pyridinium dichromate (7.18 g, 19.1 mmol) and catalytic amount of crushed 4 Å molecular sieves and a catalytic amount of acetic acid were added. The reaction was stirred overnight and then diluted with diethyl ether and stirred for approximately 2 hours. The slurry was filtered through celite and the solvent was removed "in vacuo." Quick suction chromatography yielded 1.47 g (88.5 %) of an oil: Rf 0.62 (20% ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.95 (m, 2 H), 7.50 (m, 3

H), 5.81 (m, 1 H), 5.01 (m, 2 H), 2.97 (t, 2 H, J = 7.4 Hz), 2.17(m, 2 H), 1.85 (m, 2 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 200.18, 138.02, 137.04, 132.89, 128.53, 127.99, 115.26, 37.68, 33.17, 23.28; IR (neat) 2934, 1686, 1448, 1232, 1001, 913, 753, 736, 690; mass spectrum (EI) m/z (relative intensity), 174 (m+, 8), 120 (46), 77 (31); analysis calculated for $C_{12}H_{14}O$: C: 82.72, H: 8.10; found: C: 82.95, H: 8.06.

Iodo-5-triphenylphosphoniumpentanenitrile

5-Iodovaleronitrile (6.00 g, 28.7 mmol) was diluted with benzene (28 mL; 1.0 M) and triphenylphosphine (15.0 g, 57.4 mmol) was added. The solution was refluxed overnight, and a white precipitate was formed. The slurry was filtered and washed with benzene, and dried to give 11.9 g (88 %) of a white fluffy solid: 300 MHz $^1H$ NMR ($CDCl_3$) δ 7.80 (m, 15 H), 3.82 (m, 2 H), 2.62 (t, 2 H, J = 6.9 Hz) 2.12 (m, 2 H), 1.86 (m, 2 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 135.24, 133.76, 133.63, 120.69, 130.53, 119.28, 118.31, 117.18, 25.64, 25.41, 22.79, 22.11, 21.44, 21.39, 16.95; mass spectrum (EI) m/z (relative intensity), no m+ observed, 262 (100), 183 (45); analysis calculated for $C_{23}H_{23}INP$: C: 58.61, H: 4.92; found: C: 58.77, H: 4.94.

(E,Z)-6-Phenyl-5,11-dodecadienenitrile (126)

Wittig salt (654.3 mg, 1.32 mmol) was placed in a flame dry flask and diluted with THF (1.7 mL; 0.77 M). The slurry was cooled to 0 °C and n-BuLi (0.495 mL, 1.14 mmol) was added dropwise resulting in a bright orange solution. After 20 minutes the benzyl ketone 125 was diluted with a small amount of THF and then added to the solution. After 30

minutes the reaction was warmed to room temperature and allowed to stir for three days. Then the reaction was quenched with ethanol and stirred with 80 % hexanes-ether until a homogeneous mixture resulted. It was then filtered through celite. The solvent was removed in vacuo and the resulting residue purified by column chromatography to give 72 mg (52 %) of an oil as a 1:1.1 isomer mix: Rf 0.42 and 0.35 (20 % ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) $\delta$ 7.30 (m, 5 H), 5.74 (m, 1 H), 5.54 (t, 0.50 H, J = 7.3 Hz), 5.36 (t, 0.50 H, J = 7.3 Hz), 4.95 (m, 2 H), 2.51 (t, 1 H, J = 8.0 Hz), 2.34 (m, 2 H), 2.17 (t, 1 H, J = 7.4 Hz), 2.03 (m, 3 H), 1.78 (m, 1 H), 1.63 (m, 1 H), 1.40 (m, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) $\delta$ 143.38, 142.73, 142.39, 140.70, 138.59, 138.43, 128.23, 126.91, 126.76, 126.38, 126.08, 124.50, 119.63, 114.84, 114.62, 38.75, 33.52, 33.22, 29.28, 27.84, 27.36, 27.22, 25.82, 25.61, 16.65, 16.49; IR (neat) 2930, 2858, 1438, 1119, 912, 721, 700, 542; mass spectrum (EI) m/z (relative intensity), 239 (m+, 2), 144 (45), 143 (23), 129 (25), 118 (100); analysis calculated for $C_{17}H_{21}N$: C: 85.31, H: 8.84; found: C: 85.44, H: 8.89.

(E,Z)-6-Phenyl-5,11-dodecadien-1-al (127)

Nitrile 126 (72 mg, 0.300 mmol) was placed in a flask and diluted with THF (0.60 mL; 0.5 M) and cooled to -78 °C. DIBAL (diisobutylaluminium hydride) (0.90 mL, 0.90 mmol) was added dropwise to the flask. The flask was immediately warmed to O °C. After 1.5 hours it was cooled again to -78 °C and quenched by the slow addition of methanol. The mixture was diluted with ether (50 mL) and then poured into a saturated solution of Rochelle's salt and stirred vigorously for two hours. The mixture was extracted with ether and the combined ether layers

were dried over anhydrous sodium sulfate. The solvent was removed "in vacuo" and the residue purified by column chromatography to give 40 mg (55 %) of a 1:1.1 mixture of isomers: Rf 0.37 and 0.40 (20 % ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 9.82 (s, 0.50 H), 9.70 (s, 0.50 H), 7.3 (m, 5 H), 5.79 (m, 1 H), 5.61 (t, 0.50 H, J = 7.2 Hz), 5.42 (t, 0.50 H, J = 7.5 Hz), 4.95 (m, 2 H), 2.51 (m, 2 H), 2.35 (t, 2 H, J = 7.5 Hz), 2.27 (m, 1 H), 2.02 (m, 3 H), 1.81 (m, 1 H), 1.66 (m, 1 H), 1.43 (m, 2 H) ; 75 MHz $^{13}$C NMR ($CDCl_3$) δ 202.45, 202.27, 142.98, 142.23, 141.26, 141.02, 138.66, 138.50, 128.25, 128.20, 128.06, 127.63, 126.66, 126.51, 126.32, 125.93, 114.66, 114.47, 43.37, 43.26, 38.68, 33.52, 33.19, 29.22, 28.13, 27.81, 27.26, 22.42, 22.25; IR (neat) 2931, 2859, 1725, 1292, 1454, 1441, 911, 761, 701; mass spectrum (EI) m/z (relative intensity), 242 (m+, 0.85), 144 (60), 129 (50), 105 (100), 91 (43), accurate mass calculated for $C_{17}H_{22}0$: 242.1670; found: 242.1663.

Cyclopentanols (128, 129)

Aldehyde 127 (93 mg, 0.384 mmol) was dissolved in benzene (9.0 mL; 0.1 M in TBTH). TBTH (0.247 mL, 0.919 mmol) and AIBN (12 mg, 0.076 mmol) was added to the flask and the mixture was degassed for 30 minutes with a stream of argon. The degassing tube was removed and the mixture was refluxed over night. Removal of the solvent and subsequent chromatography gave 68 mg of two products (73 %).

Physical data for the high Rf isomer (128): Rf 0.60 (35:65 THF-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.22 (m, 5 H), 5.65 (m, 1 H), 4.95 (m, 2 H), 4.41 (q, 1 H, J = 3.9 Hz), 2.63 (dt, 1 H, J = 11.1, 3.3 Hz), 2.01 (m, 3 H), 1.87 (m, 3 H), 1.75 (m, 2 H), 1.45 (m, 1 H), 1.26

(m, 5 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 145.07, 139.07, 128.17, 127.95, 125.85, 114.31, 73.43, 52.26, 45.65, 35.28, 34.12, 33.68, 28.05, 26.43, 21.33; IR (neat) 3385, 2931, 2859, 1639, 1493, 1452, 991, 909, 700; mass spectrum (EI) m/z (relative intensity), 244 (m+, 1), 183 (20), 172 (20), 117 (59), 105 (20), 91 (100), accurate mass calculated for $C_{17}H_{24}0$: 244.1827; found: 244.1827.

Physical data for the low Rf isomer (129): Rf 0.40 (35:65 THF-hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 7.22 (m, 5 H), 5.76 (m, 1 H), 4.93 (m, 2 H), 3.99 (m, 1 H), 2.62 (m, 1 H), 2.46 (m, 1 H), 2.35 (m, 2 H), 2.02 (m, 3 H), 1.67 (m 5 H), 1.22 (m, 3 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 144.00, 138.86, 128.37, 128.37, 128.10, 125.98, 114.30, 77.34, 54.22, 49.09, 35.66, 34.03, 33.73, 29.24, 26.96, 22.29; IR (neat) 3345, 2932, 2861, 1494, 1452, 909, 702; mass spectrum (EI) m/z (relative intensity), 244 (m+, 0.44), 160 (43), 159 (29), 117 (31), 104 (42), 91 (100), accurate mass calculated for $C_{17}H_{24}0$: 244.1827; found: 244.1827.

8-Nonen-1,5-diol (131)

To a stirred solution of lactol 130 (1.0 g, 9.79 mmol) in THF (19.6 mL; 0.5M) at 0 °C was added a solution of 1-butenyl magnesium bromide (prepared by the addition of 1-butenyl bromide to magnesium filings) (13.0 mL, 19.58 mmol). The reaction was stirred at room temperature for 1.5 hours and was quenched with saturated solution of aqueous ammonium chloride (5 mL), and then extracted with diethyl ether. The solvent was removed under reduced pressure and the residue was purified by suction chromatography to yield 1.4 g (93 %) of a clear oil : Rf 0.22 (35:65 THF: hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 6.05 (m, 1 H), 6.79 (m, 2

H), 5.36 (t, 3 H, J = 2.1 Hz), 2.19 (m, 2 H), 1.80 (s, 1 H), 1.74 (s, 1 H), 1.50 (m, 8 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 138.59, 114.56, 70.93, 62.11, 36.48, 36.38, 32.30, 30.02, 21.76; IR (neat) 3319, 2919, 2860, 1631, 1437, 1049, 908; mass spectrum (CI) m/z (relative intensity), 159 (m+1, 73), 141 (100), exact mass calculated for $C_9H_{19}O_2$ (m+1): 159.139; found: 159.139.

1-t-Butyldimethylsiloxy-5-hydroxynon-8-ene (132)

Diol 131 (984 mg, 6.22 mmol) was diluted with methylene chloride (12.4 mL; 0.5 M). Then triethylamine (2.60 mL, 18.7 mmol), 4-dimethylaminopyridine (75.6 mg, 0.622 mmol) and t-butyldimethylsilyl chloride (1.03 g, 6.84 mmol) was added. After 2 hours the reaction was quenched with aqueous saturated sodium bicarbonate solution (5 mL) and extracted with diethyl ether. The combined ether extracts were dried over anhydrous sodium sulfate and the solvent was removed "in vacuo" to give an oil. The oil was purified by column chromatography to give 1.56 g (92 %) of a clear oil: Rf 0.78 (35:65 THF: hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 5.79 (m, 1 H), 5.96 (m, 2 H), 3.56 (t, 3 H, J = 6.3 Hz), 2.11 (m, 2 H), 1.50 (m, 8 H), 0.85 (s, 9H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 138.60, 114.68, 71.35, 63.09, 37.15, 36.14, 32.69, 30.04, 25.97, 25.93, 21.87, 18.34; IR (neat) 3357, 2930, 2858, 1471, 1462, 1255, 1100, 1005, 909, 836, 809, 755; mass spectrum (EI), m/z (relative intensity) no m+ peak observed, 85 (100), 75 (17); analysis for $C_{15}H_{32}O_2Si$ calculated: C: 66.11; H: 11.84; found C: 66.10, H: 11.80.

1-t-Butyldimethylsiloxynon-8-ene-5-one (133)

Mono-protected diol 131 (2.37 g, 8.69 mmol) was dissolved in methylene chloride (18 mL; 0.5 M). Pyridinium dichromate (6.5 g, 17.39 mmol) and ground 4 Å molecular sieves (catalytic) and acetic acid (catalytic) were added and the mixture was stirred three hours and then diluted with diethyl ether (50 mL) and allowed to stir overnight. The solution was then filtered through a plug of celite and the solvent was removed "in vacuo." The residue was purified by suction chromatography to give 2.0 g (85 %): Rf 0.73 (20 % diethyl ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 5.75 (m, 1 H), 4.94 (m, 1 H), 3.56 (t, 1 H, J = 6.3 Hz), 2.45 (t, 2 H, 6.6 Hz), 2.39 (t, 2 H, 7.5 Hz), 2.28 (m, 2 H), 1.57 (m, 2 H), 1.46 (m, 2 H), 0.85 (s, 9 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 210.14, 137.14, 115.12, 62.78, 42.57, 41.69, 32.21, 27.75, 25.94, 25.90, 20.25, 18.29; IR (neat) 2930, 2857, 1716, 1471, 1462, 1361, 1255, 1099, 1005, 912; mass spectrum (EI), m/z (relative intensity) 270 (m+, 2), 213 (51), 171 (26), 129 (83), 115 (31); analysis for $C_{15}H_{30}O_2Si$ calculated: C: 66.61; H: 11.18; found C: 66.61, H: 11.27.

(E,Z)-1-t-Butyldimethylsiloxy-5-benzylidenenon-8-ene (134)

Benzyltriphenylphosphonium bromide (6.72 g, 15.5 mmol) was dissolved in THF (15.5 mL; 1 M) and cooled to 0 °C. Then n-butyl lithium (5.4 mL, 13.6 mmol) was added dropwise and the solution turned bright red. After 30 minutes, ketone 133 (1.05 g, 3.88 mmol), dissolved in a small amount of THF, was added to the wittig and the solution was refluxed overnight. The reaction was quenched with ethanol, and then diluted with ether. Suction chromatography yielded 1.13 g (85.0 %) of an

oil. Physical data are for the 1:1 mixture of syn and anti isomers: Rf 0.79 (10 % diethyl ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 6.27 (s, 1 H), 5.77 (m, 1 H), 4.96 (m, 2 H), 3.62 (t, 1 H, J = 5.7 Hz), 3.54 (t, 1 H, J = 5.7 Hz), 2.20 (m, 6 H), 1.50 (m, 4 H), 0.870 (d, 9 H, J = 6.0 Hz), 0.015 (d, 6 H, J = 10 Hz); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 142.60, 142.54, 138.56, 138.49, 138.30, 133.94, 129.05, 128.72, 128.50, 128.13, 126.00, 125.72, 125.62, 114.72, 114.64, 63.08, 62.81, 37.03, 36.51, 32.88, 32.56, 32.60, 32.46, 30.43, 30.00, 26.24, 26.08, 26.04, 24.52, 24.43, 18.45, 18.40; IR (neat) 2956, 2848, 1643, 1472, 1249, 1096; mass spectrum (EI), m/z (relative intensity) 344 (m+, 0.69), 288 (20), 287(77); analysis for $C_{22}H_{36}OSi$ calculated: C: 76.68; H: 10.53; found C: 76.43, H: 10.32.

(E,Z)-5-Benzylidiene-non-8-ene-1-ol (135)

Protected alcohol 134 (1.09 g, 3.16 mmol) was dissolved in THF (2.11 mL; 0.50 M) and cooled to 0 °C. Tetrabutylammonium fluoride (3.81 mL, 3.81 mmol) was added dropwise to the solution and the reaction was warmed to room temperature. After two hours the reaction was quenched with aqueous saturated sodium bicarbonate solution (5 mL) and extracted with diethyl ether. The combined extracts were dried over anhydrous sodium sulfate and concentrated "in vacuo." Subsequent chromatography yielded 616 mg (85.0 %) of an oil as a 1:1 mixture of syn and anti isomers: Rf 0.60 (35:65 THF: Hexanes) ; 300 MHz $^1$H NMR ($CDCl_3$) δ 7.25 (m, 5 H), 6.30 (s, 1 H), 5.82 (m, 1 H), 5.01 (m, 2 H), 3.69 (t, 1 H, J = 6.0 Hz), 3.59 (t, 1 H, J = 6.3 Hz), 2.25 (m, 6 H), 1.59 (m, 5 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 142.36, 142.32, 138.49, 138.39, 138.36, 138.24, 128.65, 128.11, 126.01, 125.75, 125.67, 114.71,

114.64, 62.76, 62.56, 36.93, 36.37, 32.62, 32.49, 32.37, 30.35, 29.94, 24.40, 24.31; IR (neat) 3346, 2933, 2862, 1069, 911, 734, 698; mass spectrum (EI), m/z (relative intensity) 320 (m+, 6.20), 129 (100), 115 (25), 91 (40) ; analysis for $C_{16}H_{22}O$ calculated: C: 83.43; H: 9.63; found C: 83.30, H: 9.68.

(E,Z)-5-Benzylidiene-non-8-ene-1-al (136)

Crude alcohol alkene 135 (675 mg, 2.93 mmol) was dissolved in methylene chloride. Pyridinium dichromate (2.20 g, 5.86 mmol), catalytic amount of acetic acid and ground 4 Å molecular sieves were added and the mixture was stirred at room temperature for 1.5 hours. The solution was diluted with ether and stirred overnight. The mixture was filtered through celite and the solvent was removed "in vacuo." The residue was subjected to suction chromatography and a clear oil was isolated (52 % for 2 steps). Physical data are for the 1:1 mixture of syn and anti isomers: Rf 0.40 (35:65 THF:Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 9.80 (t,0.50H, J = 1.5 Hz), 9.69 (t, 0.50 H, J = 1.2 Hz), 7.24 (m, 5 H), 6.32 (d, 1 H, J = 12.6 Hz), 5.80 (m, 1 H), 5.01 (m, 2 H), 2.50 (d of t, 1 H, J = 7.3 Hz, 1.4 Hz), 2.26 (m, 7 H), 1.84 (m, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 202.32, 201.99, 141.29, 141.29, 141.26, 138.16, 138.01, 128.59, 128.14, 126.49, 126.47, 126.16, 114.81, 114.74, 43,53, 43.34. 36.33, 36.14, 32.40, 32.25, 29.86, 29.75, 20.54, 20.45; IR (neat) 2933, 1725, 7640, 1445, 914, 747, 699 ; mass spectrum (EI), m/z (relative intensity) 228 (m+, 12), 169 (97), 143 (100), 141 (71); analysis for $C_{16}H_{20}O$ calculated: C: 84.16, H: 8.83; found: C: 83.88, H: 8.85.

(E,Z)-Methyl 3-(4-t-butyldimethylsiloxybutyl)-2,6-heptadieneoate (137)

Sodium hydride (395 mg, 9.88 mmol) was placed in a flame-dry flask, washed three times with pentane, and diluted with THF (2.5 mL). Then methyl diethylphosphonoacetate (1.7 mL, 9.29 mmol) was added dropwise to the flask. The mixture was stirred for 15 minutes and then ketone 133 (838 mg, 3.09 mmol) diluted with THF (0.5 mL) and added to the flask. The mixture was refluxed overnight and quenched with water (2 mL). Extraction and subsequent evaporation of the dried solvent gave an oil. The oil was subjected to column chromatography to yield 520 mg (54 %) of product and 350 mg of recovered starting material. Physical data are for a 1:1 mix of isomers: Rf 0.68 (20 % diethyl ether-hexanes); 300 MHz $^{1}H$ NMR ($CDCl_3$) $\delta$ 5.80 (m, 1 H), 5.60 (d, 1 H, J = 3.9 Hz), 4.97 (m, 2 H), 3.63 (s, 1.5 H), 3.63 (s, 1.5 H), 3.57 (m, 2 H), 2.62 (m, 2 H), 2.19 (m, 4 H), 1.49 (m, 4 H), 0.849 (s, 4.5 H), 0.845 (s, 4.5 H), 0.00 (s, 6 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 166.75, 163.73, 163.59, 137.98, 137.29, 115.32, 114.72, 62.83, 62.69, 50.72, 38.14, 37.41, 32.83, 32.66, 32.32, 31.69, 31.67, 31.40, 25.94, 25.90, 24.73, 23.83, 18.29; IR (neat) 2930, 2858, 1720, 1642, 1471, 1462, 1434, 1386, 1255, 1229, 1191, 1168, 1148, 1102, 1031, 1006, 912, 836, 810, 776; mass spectrum (CI), m/z (relative intensity) 327 (m+1, 100), 295 (93), 269 (48), 209 (35); accurate mass for $C_{18}H_{35}SiO_3$ calculated: 327.2355; found: 327.2340.

Methyl 3-(4-hydroxybutyl)-2,6-heptadieneoate (138)

Protected alcohol alkene (137) (1.18 g, 3.74 mmol) was dissolved in THF (3 mL, 2.24 M) and cooled to 0 °C. Then tetrabutylammonium

fluoride (4.86 mL, 4.86 mmol) was added dropwise to the cooled solution. The reaction was allowed to warm up to room temperature and was monitored by TLC very closely. After the reaction was complete, it was quenched with saturated aqueous solution of ammonium chloride (2 mL). The reaction was extracted with ether and the combined layers were dried over anhydrous sodium sulfate. Removal of the solvent "in vacuo" yielded an oil. Column chromatography gave 657 mg (83 %) of an oil. Physical data are for a 1:1 mix of isomers: Rf 0.41 (35:65 THF-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 5.83 (m, 1 H), 5.67 (s, 0.50 H), 5.65 (s, 0.50 H), 5.01 (m, 2 H), 3.70 (m, 2 H), 3.68 (s, 3 H), 2.70 (m, 2 H), 2.60 (m, 2 H), 2.21 (m, 4 H), 1.58 (m, 4 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 166.96, 166.78, 164.15, 163.58, 137.87, 137.14, 115.28, 115.01, 114.72, 62.13, 61.72, 50.83, 50.75, 38.04, 37.58, 32.58, 32.20, 32.11, 31.53, 31.47, 31.33, 24.58, 23.71; IR (neat) 3389, 2931, 2860, 1707, 1637, 1431, 1372, 1225, 1195, 1161, 1061, 1025, 908; mass spectrum (EI), m/z (relative intensity) 212 (m+, 0.76), 181 (25), 180 (24), 152 (30); accurate mass (CI) for $C_{12}H_{21}O_3$ (m+1) calculated: 213.1490; found: 213.1487.

(E,Z)-Methyl 3-(4-butanal)-2,6-heptadieneoate (139)

Alcohol (138) (572 mg, 2.73 mmol) was dissolved in methylene chloride (5.0 mL; 0.54 M) and pyridinium dichromate (2.00 g, 5.46 mmol) was added. Catalytic amounts of crushed 4 Å molecular sieves, and acetic acid were added. The reaction was stirred overnight and then diluted with a large volume of diethyl ether and allowed to stir for 4 hours. The slurry was filtered through celite and the resulting liquor was evaporated to give a residue which was then purified by column chromatography to give 330 mg

of an oil (58 %). Physical data are for a 1:1 mix of isomers: Rf 0.76 (35:65 THF-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 9.70 (m, 1 H), 5.75 (m, 1 H), 5.62 (s, 0.50 H), 5.59 (s, 0.50 H), 4.94 (m, 2 H), 3.61 (s, 1.5 H), 3.60 (s, 1.5 H), 2.59 (m, 2 H), 2.42 (q, 2 H, J = 7.5 Hz), 2.17 (m, 4 H), 1.70 (m, 2 H); 75 MHz $^{13}$C NMR δ 202.05, 201.38, 166.63, 166.50, 162.31, 162.19, 137.73, 137.05, 116.04, 115.99, 115.42, 114.90, 50.82, 43.45, 43.01, 37.30, 32.56, 31.56, 31.23, 31.14, 20.80, 19.75; IR (neat) 2948.4, 1720.1, 1642.3, 1434.8, 1231.7, 1193.3, 1188.9, 1032.9, 915.2; mass spectrum (CI) m/z (relative intensity) 211 (m + 1, 23), 207 (29), 193 (100), 179 (32), 133 (50); accurate mass for $C_{12}H_{19}O_3$ (m + 1) calculated: 211.1334; found: 211.1314.

Phenyl spiro products (140, 141, 142)

Aldehyde 136 (120 mg, 0.526 mmol) was dissolved in benzene (16 mL; 0.1 M). TBTH (0.340 mL, 1.26 mmol) and AIBN (17 mg, 0.105 mmol) were added. The mixture was degassed with a stream of argon for 30 minutes. After removing the degassing tube, the solution was heated at 80 °C overnight. Removal of the solvent "in vacuo" and column chromatography of the residue gave 120 mg of 1:1:1.2:0.4 isomeric mix of an oil (98 %). Further purification was necessary to separate individual isomers.

Physical data are for isomer 140: Rf 0.32 (20 % Ether:Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.31 (m, 1 H), 2.32 (m, 2H), 1.97 (m, 2 H), 1.50 (m, 4H), 1.27 (m, 4 H), 1.09 (d, 1 H, J = 7.8 Hz), 0.81 (d, 3 H, J = 6.0 Hz); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 141.16, 129.05, 128.14, 126.20, 75.29, 61.56, 55.79, 39.46, 37.11, 32.98,

31.83, 30.62, 19.03, 18.69; IR (neat) 3443, 2952, 2865, 1452, 1064, 703; mass spectrum (EI), m/z (relative intensity) 230 (m+, 18), 212 (83), 170 (100), 157 (34), 139 (23), 118 (27), 117 (35), 115 (28), 97 (36) accurate mass for $C_{16}H_{22}O$ calculated: 230.1670 ; found: 230.1673.

Physical data are for isomer 141: Rf 0.28 (20 % Ether:Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.82 (t, 1 H, J = 4.8 Hz), 2.82 (d, 1 H, J = 11.1 Hz), 2.22 (m, 1 H), 1.92 (m, 2 H), 1.51 (m, 6H), 1.34 (m, 2 H), 1.29 (d, 1 H, J = 5.4 Hz), 0.89 (d, 3 H, J = 6.6 Hz); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 129.65, 128.02, 125.92, 82.38, 58.22, 58.06, 42.62, 38.43, 33.31, 33.03, 20.44, 18.86; IR (neat) 3418, 2949, 2865, 702 ; mass spectrum (EI), m/z (relative intensity) 230 (73), 161 (29), 157 (24), 139 (48), 129 (29), 117 (33), 115 (27), 97 (50), 91 (72), 84 (100), accurate mass for $C_{16}H_{22}O$ calculated: 230.1670; found: 230.1671.

Physical data are for an inseparable 3:1 mixture of isomeric products 142: Rf 0.19 (20 % Ether-Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 3.86 (d, 0.25 H, J = 5.0 Hz), 3.65 (t, 0.5 H, J = 8.2 Hz), 3.27 (d, 0.15 H, J = 7.29 Hz), 2.69 (d, 0.15 H, J = 7.29 Hz), 2.46 (d, 0.50 H, J = 11.5 Hz), 2.32 (m, 0.50 H), 2.0 (m, 3 H), 1.50 (m, 8 H), 0.97 (m, 1 H), 0.91 (d, 2 H, J = 6.3 Hz), 0.70 (m, 1 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 18.31, 18.89, 20.67, 29.94, 30.01, 31.11, 31.44, 32.23, 32.36, 33.35, 36.64, 37.95, 38.15, 38.80, 54.19, 56.41, 58.54, 76.07, 79.86, 80.63, 126.07, 127.64, 127.86, 129.55, 130.22, 140.64, 142.28; IR (neat) 3382, 2953, 2869, 1453, 1077, 702; mass spectrum (EI), m/z (relative intensity) 230 (m+, 60), 212 (27), 170 (36), 157 (44), accurate mass calculated for $C_{16}H_{22}O$: 230.1670; found: 230.1673.

Ester spiro compounds (143, 144)

Aldehyde 139 (132 mg, 0.628 mmol) was dissolved in benzene (19 mL; 0.08 M in TBTH). TBTH (0.405 mL, 1.51 mmol) and AIBN (21 mg, 0.13 mmol) were added and the mixture was degassed for 30 minutes with a stream of argon. The degassing tube was removed and the reaction was refluxed overnight. The solvent was then removed and the residue purified by column chromatography to give 73 mg of approximate 3:1:1:0.5:0.5 isomeric mix of an oil (55 %). Only one compound was isolated pure; the other four were isolated and characterized as a mixture.

Physical data are for pure top isomer (143): Rf 0.36 (35:65 THF-hexanes); 300 MHz $^{1}H$ NMR ($CDCl_3$) $\delta$ 3.75 (m, 1 H), 3.73 (s, 3 H), 2.84 (d, 1 H, J = 3.0 Hz), 2.22 (m, 2 H), 2.13 (m, 1 H), 1.88 (m, 3 H), 1.59 (m, 3 H), 1.30 (m, 3 H), 1.00 (d, 3 H, J = 6 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$) $\delta$ 177.39, 76.73, 60.50, 55.92, 51.78, 40.88, 37.89, 33.35, 30.05, 23.41, 18.85, 18.24; IR (neat) 3524, 2952, 2869, 1714, 1436, 1373, 1301, 1268, 1198, 1160, 1082.

Physical data are for bottom 1:1:0.5:0.5 isomer mix (144): Rf 0.26 (35:65 THF-hexanes); 300 MHz $^{1}H$ NMR ($CDCl_3$) $\delta$ 3.80 (m, 1 H), 3.64, 3.607, 3.58, 3.57 (s, 3 H), 3.00, 2.66 (d, 1 H, J = 6.9 Hz, 5.1 Hz), 2.30 (m, 2 H), 1.84 (m, 3 H), 1.63 (m, 2 H), 1.47 (m, 3 H), 1.19 (m, 2 H), 0.948 (m, 3 H); IR (neat) 3454, 2953, 2870, 1731, 1453, 1435, 1376, 1269, 1195, 1158, 1091, 1039, 733; mass spectrum (CI), m/z (relative intensity) 213 (m+1, 16), 195 (100); accurate mass for $C_{12}H_{21}O_3$ (m+1) calculated: 213.1490; found: 213.1491.

(E,Z)-9-Phenyl-1,8-nonadiene-4-ol (148)

Aldehyde 147 (283 mg, 1.62 mmol) was dissolved in THF (0.5 mL) and saturate aqueous ammonium chloride (2.11 mL; 0.76 M). Then allyl bromide (0.184 mL, 2.11 mmol) and zinc dust (138 mg, 2.11 mmol) were added and the mixture was stirred open to the atmosphere for 3 hours. The mixture was extracted with diethyl ether and the combined layers were dried over anhydrous sodium sulfate. The solvent was removed "in vacuo" and the residue was purified by column chromatography to give 278 mg of an oil (80 %). Physical data are for a 2.3:1 mix of isomers: Rf 0.25 (35:65 THF-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.39 (m, 1 H), 6.24 (dt, 0.66 H, J = 15.9 Hz,6.9 Hz), 5.84 (m, 1 H), 5.68 (dt, 0.33 H, J = 11.2 Hz, 7.2 Hz), 5.14 (m, 2 H), 3.70 (m, 1 H), 2.31 (m, 3 H), 2.17 (m, 1 H), 1.68 (m, 2 H). 1.55 (m, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 137.81, 137.71, 134.89, 132.72, 130.64, 130.15, 129.15, 128.77, 128.51, 128.16, 126.88, 126.53, 125.97, 118.06, 70.59, 70.49, 42.01, 36.35, 36.31, 32.99, 28.52, 26.02, 25.45; IR (neat) 3383, 3024, 2031, 2859, 1494, 1447, 995, 964, 914, 693; mass spectrum (EI), m/z (relative intensity) 217 (m+, 8), 199 (27), 176 (30),175 (100); accurate mass for $C_{15}H_{21}O$ calculated: 217.1592; found: 217.1590.

(E,Z)-9-Phenyl-1,8-nonadiene-4-one (149)

Alcohol 148 (61.0 mg, 0.281 mmol) was dissolved in methylene chloride (1 mL; 0.3 M) and pyridinium dichromate (212 mg, 0.563 mmol) was added. A catalytic amount of crushed 4 Å molecular sieves was added and the mixture was stirred overnight. The mixture was diluted with ethyl ether and then filtered through celite. The solvent was removed "in vacuo"

and the residue was purified by column chromatography to yield 31 mg (52 %) of an oil. Physical data are for a 2.3:1 mix of isomers. Rf 0.48 (20 % ether-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.30 (m, 5 H), 6.33 (d, 0.33 H, J = 11.7 Hz), 6.28 (d, 0.66 H, J = 15.8 Hz), 6.06 (dt, 0.66 H, J = 15.8 Hz, 6.9 Hz) 5.79 (m, 1 H), 5.50 (dt, 0.33 H, J = 11.7 Hz, 7.3 Hz), 5.05 (m, 2 H), 3.02 (dd, 2 H, J = 13.9 Hz, 7.0 Hz), 2.35 (dt, 2 H, J = 12.6 Hz, 7.3 Hz), 2.22 (dq, 1 H, J = 7.4 Hz, 1.8 Hz), 2.11 (m, 1 H), 1.66 (m, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 208.49, 208.41, 137.57, 137.48, 131.85, 130.70, 130.67, 129.80, 129.71, 128.73, 128.62, 128.51, 128.27, 128.18, 127.00, 126.52, 125.98, 118.72, 47.81, 47.75, 41.56, 41.42, 32.31, 27.86, 23.73, 23.11; IR (neat) 2933, 1715, 1493, 1447, 966, 918, 694; mass spectrum (CI), m/z (relative intensity) 215 (100, m+1), 214 (31), 213 (19), 197 (99); accurate mass for $C_{15}H_{19}O$ (m+1) calculated: 215.1435; found: 215.1439.

(E,Z)-Methyl 7-hydroxy-2,9-decadienoate (151)

Lactol 150 (706 mg, 5.97 mmol) was dissolved in chloroform (12 mL; 0.50 M). A catalytic amount of benzoic acid and methyl(triphenylphosphoranylidene)acetate (4.40 g, 13.1 mmol) were added to the reaction. After stirring overnight, the reaction was diluted with diethyl ether and filtered through celite. The solvent was removed "in vacuo" and the resulting residue purified by suction chromatography to give 910 mg of an oil (77.0 %). Physical data are for a 15:1 mixture of trans to cis isomers. Rf 0.56 (10 % Hexanes-Ether); 300 MHz $^1$H NMR ($CDCl_3$) δ 6.97 (dt, 1 H, J = 15.9 Hz, 6.9 Hz), 5.84 (m, 2 H), 5.13 (m, 2 H), 3.72 (s, 3 H), 3.68 (bs, 1 H), 2.23 (m, 4 H), 1.57 (m, 5 H); 75

MHz $^{13}C$ NMR ($CDCl_3$) δ 167.04, 149.21, 134.62, 121.06, 118.04, 70.25, 51.32, 41.97, 36.05, 32.03, 24.08; IR (neat) 3439, 2934, 1724, 1656, 1437, 1314, 1274, 1202, 1038, 915, 733; mass spectrum (CI), m/z (relative intensity) 199 (100, m+1), 181 (72); Analysis for $C_{11}H_{18}O_3$ calculated: C: 66.64, H: 9.15; found: C: 66.61, H: 9.17.

(E,Z)-Methyl 7-oxo-2,9-decadieneoate (152)

Alcohol 151 (760 mg, 3.83 mmol) was dissolved in methylene chloride (7.6 mL; 0.50 M). Then, pyridinium dichromate (2.89 g, 7.67 mmol) and catalytic amount of acetic acid and ground 4 Å molecular sieves were added to the reaction mixture. After stirring overnight, the reaction was diluted with diethyl ether and filtered through celite. The solvent was removed "in vacuo" and the resulting residue purified by suction chromatography to give 525 mg of an oil (70.0 %): Rf 0.64 (10 % Hexanes-Ether); 300 MHz $^1H$ NMR ($CDCl_3$) δ 6.97 (dt, 1 H, J = 15.6 Hz, 6.9 Hz), 5.84 (m, 2 H), 5.13 (m, 2 H), 3.64 (s, 3 H), 3.16 (dt, 2 H, J = 7.0 Hz, 1.26 Hz), 2.22 (q, 1 H, J = 7.2 Hz), 2.21 (q, 1 H, J = 7.31 Hz), 1.76 (m, 2 H); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 207.69, 166.72, 148.25, 130.41, 121.47, 118.73, 51.27, 47.66, 40.99, 31.21, 21.63; IR (neat) 2951, 1720, 1657, 1437, 1408, 1315, 1207, 1178, 1027, 980, 921; mass spectrum (EI), m/z (relative intensity) 196 (m+, 1) 165 (41), 155 (80), 127 (39), 123 (95), 95 (100), 85 (87), 81(43), 71 (43), 69 (39), 68 (53), 67 (59), 59 (67), 55 (53); analysis for $C_{11}H_{16}O_3$ calculated: C: 67.32, H: 8.22; found: C: 67.11, H: 8.17.

Bicyclic products (153, 154)

Ketone 152 (127 mg, 0.648 mmol) was dissolved in benzene (6.5 mL; 0.10 M). TBTH (0.436 mL, 1.62 mmol) and AIBN (21.0 mg, 0.129 mmol) was added and the mixture was degassed with a stream of argon. The reaction was heated at 80 °C overnight. The solvent was removed "in vacuo" and the resulting residue purified by column chromatography to give a total of 111 mg of oil. The highest Rf spot could not be identified. The lower 2 spots (68.9 mg, 54.2 %) were identified as bicyclic products and were present in approximately a 1:1 ratio.

Physical data for 153 are as follows: Rf 0.32 (20% THF-Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 3.60 (s, 3 H), 2.80 (s, 1 H), 2.55 (dd, 1 H, J = 2.1 Hz, 6.9 Hz), 2.39 (m, 2 H), 2.00 (m, 3 H), 1.67 (m, 4 H), 1.24 (m, 1 H), 0.99 (d, 3 H, J = 6.6 Hz); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 176.72, 90.26, 55.94, 54.65, 51.34, 48.92, 42.04, 36.89, 33.20, 25.88, 16.21; IR (neat) 3454, 2944, 2861, 1730, 1433, 1368, 1273, 1201, 1160, 994; mass spectrum (EI), m/z (relative intensity) no m+ observed, 156 (50), 125 (36), 124 (54), 97 (55), 69 (58), 55 (58); accurate mass (CI) for $C_{11}H_{19}O_3$ (m+1) calculated: 199.1334; found: 199.1317.

Physical data for 154 are as follows: Rf 0.21 (20% THF-Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 3.70 (s, 3 H), 2.45 (m, 2 H), 2.05 dd, 1 H, J = 6.0 Hz, 13.5 Hz), 1.91 (dd, 1 H, 9.3 Hz, 10.8 Hz), 1.80 (m, 2 H), 1.60 (m, 2 H), 1.45 (m, 1 H), 1.31 (t, 2 H, J = 12.9 Hz), 1.02 (d, 3 H, J = 6.6 Hz), 0.89 (m, 1 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 175.61, 90.17, 59.45, 57.60, 51.60, 49.84, 41.20, 38. 74, 31.30, 25.57, 17.91; IR (neat) 3437, 2952, 2868, 1736, 1436, 1377, 1310, 1292, 1213, 1170, 1027; mass spectrum (EI), m/z (relative intensity),198 (m+, 4), 156 (100), 139 (62), 124 (71), 121 (25), 100 (44), 97 (85), 83 (28), 69 (27);

Analysis for $C_{11}H_{18}O_3$ calculated: C: 66.64, H: 9.15; found: C: 66.76, H: 9.17.

(E,Z)-3,3-Dimethyl-9-phenyl-1,8-nonadiene-4-ol (155)

Aldehyde 147 (400 mg, 2.29 mmol) was dissolved in THF (0.5 mL) and saturated aqueous ammonium chloride (2.29 mL; 1.0 M) was added. Then prenyl bromide (0.344 mL, 2.98 mmol) and zinc dust (195 mg, 2.98 mmol) were added and the mixture was stirred open to the atmosphere for 3 hours. The mixture was extracted with diethyl ether and the combined layers were dried over anhydrous sodium sulfate. The solvent was removed "in vacuo" and the residue was purified by column chromatography to give 472 mg of an oil (84 %). Physical data are for a 2.3:1 mix of isomers: Rf 0.25 (35:65 THF-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 6.25 (m, 1 H), 6.11 (dt, 0.66 H, J = 15.9 Hz, 6.6 Hz), 5.69 (dt, 1 H, J = 17.4 Hz, 10.8 Hz), 5.55 (dt, 0.33 H, J = 11.7 Hz, 7.2 Hz), 4.95 (m, 2 H), 3.15 (dd, 0.66 H, J = 10.5 Hz, 3.3 Hz), 3.09 (dd, 0.33 H, J = 10.2 Hz, 3.0 Hz), 2.22 (m, 2 H), 1.56 (m, 5 H), 1.20 (m, 1 H), 0.920 (s, 3.96 H), 0.880 (s, 1.98 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 145.48, 137.90, 132.90, 130.82, 130.05, 129.03, 128.80, 128.50, 128.15, 126.84, 126.50, 125.98, 113.31, 78.13, 78.06, 41.74, 41.71, 33.03, 31.03, 30.99, 28.58, 27.41, 26.83, 23.10, 23.06, 23.03, 22.22; IR (neat) 3454, 2944, 2865, 1493, 1448, 1073, 965; mass spectrum (CI), m/z (relative intensity) 245 (m+1, 17), 227 (99), 176 (59), 175 (64); accurate mass for $C_{17}H_{25}O$ (m+1) calculated: 245.1905; found: 245.1900.

(E,Z)-3,3-Dimethyl-9-phenyl-1,8-nonadiene-4-one (156)

Alcohol 155 (256 mg, 1.04 mmol)was dissolved in methylene chloride (4 mL; 0.25 M) and pyridinium dichromate (788 mg, 2.09 mmol) was added. Catalytic amounts of crushed 4 Å molecular sieves and acetic acid was added and the mixture was stirred overnight. The mixture was diluted with ethyl ether and then filtered through celite. The solvent was removed "in vacuo" and the residue was purified by column chromatography to yield 118 mg of and oil (47 %). Physical data are for a 2:1 mix of isomers: Rf 0.83 (35:65 THF-hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 7.20 (m, 5 H), 6.33 (d, 0.33 H, J = 11.6 Hz), 6.27 (d, 0.66 H, J = 15.8 Hz), 6.06 (dt, 0.66 H, J = 15.8 Hz, 6.8 Hz), 5.7 (m, 1 H), 5.51 (dt, 0.33 H, J = 11.0 Hz, 5.0 Hz), 5.05 (m, 2 H), 2.38 (m, 2 H), 2.19 (m, 1 H), 2.07 (q, 1 H, J = 7.0 Hz), 1.59 (m, 2 H), 1.12 (s, 4 H), 1.09 (s, 2 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 212.76, 212.72, 142.60, 142.56, 137.68, 137.57, 132.13, 130.52, 130.07, 129.52, 128.74, 128.60, 128.49, 128.14, 126.93, 126.56, 125.97, 114.22, 50.81, 50.76, 36.78, 36.54, 32.35, 27.99, 24.15, 23.52, 23.49; IR (neat) 2970, 1708, 1447, 965, 919, 693.

(E,Z)-Methyl 8,8-dimethyl-7-hydroxy-9,2-decadieneoate (157)

Aldehyde 25 was dissolved in THF (2 mL; 5.0 M) and diluted with a saturated aqueous solution of ammonium chloride (8 mL). The reaction was preformed in an open flask. Prenyl bromide (1.25 mL, 10.8 mmol) and zinc dust (708 mg, 10.8 mmol) were added consecutively and evolution of heat was observed. The reaction was stirred for one hour and

then extracted with ether. The ether extracts were combined and evaporated to give an oil which was subjected to quick suction chromatography to yield 1.36 g (76 %) of a clear oil. Physical data are for a 6:1 mix of trans to cis isomers: Rf 0.68 (35:65 THF: Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 6.97 (dt, 1 H, J = 15.0 Hz, 6.92 Hz), 5.81 (m, 2 H), 5.08 (m, 2 H), 3.63 (s, 3 H), 3.61 (s, 0.5 H), 3.14 (dd, 1 H, J = 10.2 Hz, 2.3 Hz), 2.15 (m, 2 H), 1.70 (m, 2 H), 1.45 (m, 2 H), 1.20 (m, 1 H), 1.0 (s, 6 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 167.07, 150.67, 149.43, 145.38, 145.26, 120.92, 119.27, 113.26, 113.05, 77.85, 77.73, 51.30, 50.92, 41.62, 32.12, 30.83, 30.79, 28.75, 26.26, 25.44, 22.88, 22.84, 22.21, 22.17, 22.12; IR (neat) 3508, 2950, 2867, 1726, 1656, 1437, 1313, 1273, 1200, 1076, 1040, 984, 913; mass spectrum (EI), m/z (relative intensity) no m+ observed, 157 (35), 125 (100), 70 (96), 69 (25), 55 (30), 41 (25); analysis for $C_{13}H_{22}O_3$ calculated: C: 68.99, H: 9.80; found: C: 68.71, H: 9.70.

(E,Z)-Methyl 8,8-dimethyl-9,2-decadiene-7-one-oate (158)

Alcohol 157 (1.36 g, 6.00 mmol) was dissolved in methylene chloride (12 mL; 0.50 M). Then pyridinium dichromate (4.50 g, 12.0 mmol) and catalytic amounts of crushed 4 Å molecular sieves and acetic acid were added. The mixture was allowed to stir overnight and then diluted with diethyl ether. The resulting slurry was filtered through celite. The solvent was removed "in vacuo" and the residue purified by quick suction chromatography to give 910 mg (68 %) of an oil. Physical data are for a 6:1 mix of trans to cis isomers: Rf 0.71 (35:65 THF: Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 6.92 (dt, 1 H, J = 15.6 Hz, 6.9 Hz), 5.84 (m, 2 H), 5.13 (m, 2 H), 3.74 (s, 3 H), 3.70 (s, 0.50 H), 2.47 (t, 2 H, J = 7.1 Hz), 2.16 (m, 2 H), 1.70 (m, 2 H), 1.21 (s, 6 H); 75 MHz $^{13}$C NMR

($CDCl_3$) δ 212.14, 166.83, 148.52, 142.34, 121.36, 114.32, 51.28, 50.66, 36.22, 31.31, 28.26, 23.39, 22.08; IR (neat) 2950, 1713, 1657, 1461, 1436, 1411, 1378, 1364, 1317, 1272, 1199, 1096, 1071, 1041, 1016, 994, 920; mass spectrum (EI), m/z (relative intensity) no m+ observed, 155 (42), 127 (54), 123 (100), 95 (98), 85 (94), 69 (40), 67 (43), 41 (71); analysis for $C_{13}H_{20}O_3$ calculated: C: 69.61, H: 8.99; found: C: 69.39, H: 8.85.

Bicyclic products of Gem-methyl keto ester alkene (159, 160, 161)

Ketone 158 (159 mg, 0.709 mmol) was dissolved in benzene (14.7 mL; 0.05 M). Tributyltin hydride (0.476 mL, 1.77 mmol) and AIBN (23 mg, 0.14 mmol) were added and the mixture was degassed for 30 minutes. The degassing tube was removed and the reaction was heated to 80 °C for 18 hours. The solvent was evaporated and the crude oil subjected to column chromatography. Three products in approximate ratio of 1:1:2, collectively weighing 79 mg (58 %), and recovered starting material (23 mg) were obtained from the reaction mixture.

Physical data are for 159: Rf 0.45 (35:65 THF: Hexanes); 300 MHz $^1H$ NMR ($CDCl_3$) δ 3.66 (s, 3 H), 2.68 (m, 1 H), 2.46 (dd, 1 H, J = 6.3 Hz, 4.5 Hz), 2.15 (m, 2 H), 1.90 (m, 1 H), 1.70 (m, 3 H), 1.50 (m, 2 H), 0.925 (d, 6 H, J = 4.8 Hz), 0.875 (d, 3 H, J = 7.2 Hz); 75 MHz $^{13}C$ NMR ($CDCl_3$) δ 175.77, 94.35, 52.45, 52.17, 51.29, 45.25, 43.34, 35.56, 31.76, 24.65, 22.67, 18.08, 11.36; IR (neat) 3507, 2954, 2876, 1732, 1436, 1377, 1279, 1160; mass spectrum (CI), m/z (relative intensity) 227 (m +1, 4), 218 (81), 209 (98), 149 (100); exact mass, calculated for $C_{13}H_{23}O_3$ (m + 1): 227.1647; found: 227.1654.

Physical data are for 160: Rf 0.35 (35:65 THF: Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 3.61 (s, 3 H), 2.25 (m, 2 H), 2.00 (dd, 1 H, J = 9.3 Hz, 2.1 Hz), 1.90 (m, 1 H), 1.80 (m, 2 H), 1.40 (m, 2 H), 1.25 (m, 2 H), 0.910 (s, 3 H), 0.820 (d, 3 H, J = 6.9 Hz), 0.715 (s, 3 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 176.31, 94.33, 57.42, 55.16, 51.63, 48.63, 45.33, 35.67, 32.06, 27.20, 23.37, 19.58, 13.08; IR (neat) 3478, 2956, 2873, 1732, 1453, 1438, 1376, 1281, 1198, 1177; mass spectrum (CI), m/z (relative intensity) 227 (m+1, 3), 209 (37), 156 (20), 149 (100); exact mass, calculated for $C_{13}H_{23}O_3$ (m + 1): 227.1647; found: 227.1650 .

Physical data are for 161 (mp. 90-91 °C): Rf 0.52 (35:65 THF: Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 3.66 (s, 3 H), 2.50 (dt, 1 H, J = 11.7 Hz, 3.8 Hz), 1.90 (m, 1 H), 1.70 (m, 5 H), 1.50 (m, 4 H), (1.20, 1 H), 1.03 (s, 1 H), 1.00 (s, 3 H), 0.898 (s, 3 H); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 176.75, 83.69, 51.33, 43.82, 43.44, 36.55, 35.13, 32.60, 26.54, 25.67, 25.52, 22.82, 19.52; IR (neat) 3515, 2970, 2948, 2872, 1713, 1449, 1439, 1372, 1320, 1274, 1209, 1179, 1164, 1136, 992; mass spectrum (CI), m/z (relative intensity) 227 (m + 1, 76), 218 (97), 209 (100); exact mass, calculated for $C_{13}H_{23}O_2$ (m + 1): 227.1647; found: 227.1654.

Sm $I_2$Bicyclic products of Gem-methyl keto ester alkene (159, 160, 171, 172): Method A

Samarium metal (559 mg, 3.72 mmol) was placed in a flame-dried flask and diluted with THF (2 mL). Then methylene iodide (0.240 mL, 2.98 mmol) was added and the solution was gently warmed with a heat gun for 30 seconds. After 3 minutes the reaction became very exothermic and refluxed. After 1 hour, the solution was diluted with THF (3 mL; 0.1 M)

and stirred for an additional hour at room temperature. The solution was cooled to -78 °C and a mixture of ketone 158 (167 mg, 0.744 mmol) and t-butanol (0.140 mL, 1.49 mmol) in of THF (0.5 mL) was added dropwise to the cooled solution. The solution was allowed to warm up to room temperature and was stirred at that temperature overnight. The reaction was first diluted with diethyl ether and then quenched with water (1 mL) and the mixture was stirred with celite for 2 hours. The slurry was filtered through celite and the solvent was removed "in vacuo" to give and oil which was subjected to column chromatography. Four products in a 3.8: 1: 1.2: 6.0 ratio, weighing 138 mg (82 %) were obtained. Two of the products (159 and 160) were previously isolated and are described above.

Physical data are for 171: Rf 0.48 (35:65 THF: Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 6.07 (dd, 1 H, J = 6.6 Hz, 10.8 Hz), 5.04 (m, 2 H), 3.65 (s, 3 H), 2.73 (dd, 1 H, J = 10.8 Hz, 4.2 Hz), 2.36 (m, 1 H), 2.00 (m, 3 H), 1.73 (m, 2 H), 1.60 (m, 1 H), 1.35 (m, 1 H), 1.12 (d, 6 H, J = 18.3 Hz); 75 MHz $^{13}$C NMR ($CDCl_3$) δ 173.54, 145.80, 112.37, 86.57, 51.51, 46.52, 43.27, 37.35, 32.30, 30.23, 24.47, 22.82, 20.45; IR (neat) 3519, 2966, 2876, 1731, 1469, 1436, 1377, 1294, 1143; mass spectrum (EI), m/z (relative intensity) 227 (m+1, self CI, 2), 209 (86), 157 (35), 139 (23), 135 (24), 125 (100), 97 (41), 70 (47), 69 (72), 55 (57); accurate mass (CI) for $C_{13}H_{23}O_3$ (m + 1) calculated: 227.1647; found: 227.1640.

Physical data are for 172: Rf 0.52 (35:65 THF: Hexanes); 300 MHz $^1$H NMR ($CDCl_3$) δ 5.88 (dd, 1 H, J = 6.9 Hz, 10.8 Hz), 5.09 (m, 2 H), 2.75 (m, 2 H), 2.24 (dd, 1 H, J = 18 Hz, 2.1 Hz), 1.70 (m, 6 H), 1.09 (d, 6 H, J = 1.8 Hz) 75 MHz $^{13}$C NMR ($CDCl_3$) δ 177.63, 142.86, 114.47, 102.48, 42.50, 38.42, 37.75, 35.39, 34.65, 23.81, 22.12; IR (neat) 2969, 2873, 1769, 1196; mass spectrum (EI), m/z (relative intensity) 194 (m+,

1.7), 125 (100); exact mass, calculated for $C_{12}H_{18}O_2$ (m+): 194.1306; found: 194.1305.

Method B

Samarium metal (210 mg, 1.39 mmol) was placed in a flame dry flask and diluted with THF (5 mL). Then methylene iodide (0.072 mL, 0.892 mmol) was added and stirred vigorously. After one hour, the solution was diluted with THF (17 mL, 0.02 M) and stirred for an additional hour. HMPA (1 mL, 0.4 M) was added to this solution and cooled to -78 °C. Then ketone 158 was added and the solution turned brown immediately. The solution was diluted with ether and stirred with celite for an additional hour. A GC trace of this reaction mixture revealed the following percentages of previously isolated material: 172: 2.7%; 160: 5.9%; 159: 46.5%; 171: 29.5%.

Method C

Samarium metal (401 mg, 2.67 mmol) was placed in a flame dry flask and diluted with THF (2 mL). Then methylene iodide (0.179 mL, 2.22 mmol) was added and the mixture was stirred vigorously. After one hour THF (2.2 mL, 0.1 M) was added and stirred for and additional hour. HMPA (2.2 mL, 0.1 M) was added to this solution and cooled to -78 °C. The solution solidified almost immediately. It was warmed to room temperature and ketone 158 (100 mg, 0.445 mmol) was added to this solution. It was allowed to stir overnight. The reaction was diluted with ether and then celite was added to this solution. A GC analysis of this mixture revealed the following percentages of previously isolated material: 172: 1.8%; 160: 5.6%; 159: 61.8%; 171: 4.6%.

Method D

Samarium metal (200 mg, 1.33 mmol) was placed in a flame dry flask and diluted with THF (1 mL). Then methylene iodide (0.090 mL, 1.11 mmol) was added to the slurry and stirred vigorously. After one hour THF (1.2 mL) was added and stirred for an additional hour. It was then cooled to -78 °C and then warmed to 0 °C. Ketone 158 (50 mg, 0.222 mmol) was diluted with t-butanol (0.042 mL, 0.44 mmol) and added to the solution of samarium diiodide. The mixture was immediately warmed to room temperature and then stirred overnight. The mixture was diluted with ether and celite was added. GC analysis of this reaction mixture revealed the following percentages: 172: 0%; 160: 1.0%; 159: 11.3%; 171: 1.5%; HMPA: 80.4%.

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## BIOGRAPHICAL SKETCH

Janet Burroff was born in Atwater, California. The daughter of a military family, she would first move to Bangor, Maine, before finally settling in Bossier City, Louisiana. She grew up in this small town, flanked on one side by an air force base, and the other side by bottoms wetlands, with the romantic idea of one day becoming a nurse. She spent a great deal of time investigating the bayous with her brother, Jay, and her father, who encouraged her interest in science. She started college and quickly changed her major to medical technology, and then to chemistry. Always fascinated with the bright cobalt blue pond that was in the center of town, she found a niche in chemistry and graduated 1986 from LSU with a degree in chemistry. She then moved to Florida with her newly wed husband, Kevin. After starving for one year as a wet lab technician, the decision to further her education was easy and she embarked on a new career as an organic chemist. While in graduate school, she developed a passion for gardening, orchids, and lizards, and has become very politically active in women's rights issues and environmental causes. Now 9 years after her initial decision to enter the world of chemistry, the bright blue pond that spurred her interest in chemistry has become yet another super fund sight and she has yet another choice to make in her life. She plans to move to New Orleans to live with her husband and search for employment. The task of moving to a state which has a crook and a klansman running for governor, and finding a job during the Bush-induced economic depression will not be easy, but she is hopeful anyway. She dreams of one day owning a catfish farm and raising hell in the political world. In the meantime, however, she is content just smelling the flowers.

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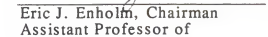

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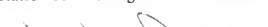

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Russell M. Bauer
Associate Professor of Clinical and Health Psychology

This dissertation was submitted to the Graduate Faculty of the Department of Chemistry in the College of Liberal Arts and Sciences and to the Graduate School and was accepted as partial fulfillment of the requirements for the degree of Doctor of Philosophy.

December, 1991

Dean, Graduate School